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Synthesis of Novel Substituted 4-[2-pyridylmethoxy]Phenyl Methylthio substiTuted Benzimidazoles and their Biological Activity

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ABSTRACT

This work presents the synthesis of a few new substituted 4-[2-pyridylmethoxy] phenyl methylthio-substituted-benzimidazole (7a–l). Substituted 2-pyridylmethyl chlorides (1a–d) are condensed with 4-hydroxy-3-methoxy benzaldehyde (2) to yield substituted 4-[2-pyridylmethoxy] benzaldehyde (3a–d). These are further reduced to substituted 4-[2-pyridylmethoxy] benzyl alcohols (4a–d), and chlorinated to corresponding substituted 4-[2-pyridylmethoxy] benzyl chlorides (5a–d). These substituted 4-[2-pyridylmethoxy] benzyl chlorides are coupled with 2-mercapto-substituted-benzimidazoles to get substituted 4-[2-pyridylmethoxy] phenylmethylthio-substituted-benzimidazoles (6a–l). All the molecules thus synthesized were characterized by IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR & Mass spectral studies and screened for their anti-bacterial and anti-fungal activities.

Keywords: 2-Mercaptobenzimadazoles; Synthesis; Characterization; Anti-fungal; Anti-bacterial

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INTRODUCTION

The development of drug molecules resistance to current anti-bacterial therapy continues to stimulate the search for more effective agents. Exclusive literature survey on benzimidazole derivatives especially 2-Mercaptobenzimidazole revealed that they have diversified biological activities such as anticonvulsant, anti-helminthes, antiamoebic, antiparasitics, potent H3 antagonist, and anxiolytic properties [1-10] General anti-microbial activity of benzimidazole derivatives has also been extensively investigated and reported. Further the pyridine moiety in a drug molecule is known as one of the important structural fragments that exhibit anticonvulsant activity [11]. 4-Hydroxy-3-methoxy Benzaldehyde (vanillin) is a primary chemical component of vanilla bean extract and has been used as an artificial flavoring agent in food and pharmaceuticals. It is also reported to exhibit a wide range of biological activities such as an anti-bacterial [12], antioxidant [13] and different synthetic procedures of this naturally occurring compound are available. A careful analysis of the reported literature clearly indicates a persistent thrust for the development of newer molecules with improved anti-microbial activity.

In the present work we have proposed examine a synergetic biological activity when the above mentioned three components such as 2-mercoptobenzimadazole, 2-pyridinylmethyl chlorides and vanillin are coupled. Thus we report here detail synthetic methodology characterization and anti- microbial investigation of few novel set of molecules based on 2-mercoptobenzimadazole, 2-pyridinylmethyl chlorides and vanillin. Anti-bacterial activity of the synthesized molecule was investigated for their inhibition against S.Aureus, E. Fecalis, S.Mutans and Klebsiella and anti-fungal activities were evaluated against A.Niger, A.Flavus and Candida.

The novelty of this work is that we have developed a systematic methodology for the synthesis of a few novel molecules with potential anti-microbial activities which to the best of our knowledge is not reported in the literature to date.

EXPERIMENTAL SECTION

The majority of the solvents were purified by distillation under nitrogen in the presence of the indicated drying agents and used fresh: dichloromethane (Calcium hydride), acetone (potassium permanganate) and Acetonitrile (phosphorous pentoxide). Reaction progress was monitored by thin-layer chromatography (TLC) using pre-coated SiO_2 gel (HF_{254} 200 mesh) aluminum plates (E Merck). Visualization was achieved with UV light. Melting points of synthesized compounds are found out using Buche apparatus with one end opened capillary tube and all melting points are uncorrected. The IR spectra of these compounds are recorded on ABB Bomen FTIR spectrometer MB 104 with KBr Pellets. ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR spectra are recorded on 300 MHz- Broker DPX 200 spectrometer, by using tetramethyl silane (TMS) as an internal standard. Chemical shifts are reported in ppm down fields from TMS. Spin multiplicities are described as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet) and m (multiplet). Coupling constants are reported in Hertz (Hz). Mass spectra were recorded on Finnigan MAT 8230 mass spectrometer at 200°C, 70 eV with trap current of 200 IA, and 4 kV acceleration voltages. Key starting materials for the preparation of substituted 4-[2-pyridylmethoxy] phenyl methylthio-substituted-benzimidazole such as 4-(2,2,2-Trifluoroethoxy)-2-(chloromethyl)-3-methylpyridine (1a), 2-(Chloromethyl)-4-methoxy-3,5-dimethylpyridine (1b), 2-(Chloromethyl)-3,4–dimethoxy pyridine (1c), 4-(3-Methoxypropoxy)-2-(chloromethyl)-3-methylpyridine (1d), 4-Hydroxy-3-methoxy benzaldehyde (2), 1H-Benzo[d]imidazole-2-thiol (6a), 5-Methoxy-1H-benzo[d] imidazole-2-thiol (6b) and 5-(Difluoro methoxy)-1H-benzo[d] imidazole-2-thiol (6c) were obtained from commercially sources like Sigma-Aldrich and SDF chemicals and used as obtained.

General procedure for preparation of 4-((4-(2, 2, 2-trifluoroethoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxybenzaldehyde, 3a-d

A mixture of Substituted 2-chloromethyl pyridine compounds (1a-d; 0.0018mol) and 4-Hydroxy-3-methoxy Benzaldehyde compound (2; 0.0021mol) was charged with 20 volumes of acetone containing potassium iodide and potassium carbonate powders. The reaction mass was stirred for 20 hours at room temperature. After TLC complies, the reaction mass was quenched with water and MDC. The MDC layer was washed with water followed by 5% Aqueous NaOH solution. The organic phase was dried with anhydrous sodium sulfate and the solvent was removed under vacuum, the residue thus obtained was treated with n-Hexane, filtered the solid, washed with n-hexane and dried to obtain the pure product 3a-d.

General procedure for preparation of (4-((4-(2, 2, 2-trifluoroethoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxyphenyl) methanol, 4a-d

0.281mol of substituted 4-((4-(2, 2, 2-trifluoro- ethoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxybenzaldehyde compounds (3a-d) was charged into methanol and to this was charged 0.425 mol of sodium borohydride. The reaction mass was stirred for 30 minutes at room temperature. After TLC complies, the reaction mass was treated with water and chilled to 10-15°C. The crystals of the title products were observed, which was filtered and dried at ambient temperature.

General procedure for preparation of 4-(2, 2, 2-trifluoroethoxy)-2-((4-(chloromethyl)-2-methoxyphenoxy) methyl)-3-methylpyridine, 5a-d

0.251mol of Substituted (4-((4-(2, 2, 2-trifluoroethoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxyphenyl) methanol derivatives ((4a-d) was charged to MDC and chilled to 5-10°C. To this solution, 0.315mol of thionyl chloride was added slowly. The reaction mass was stirred for 2 hours at 10-15°C. After the TLC complies, the solution was concentrated under reduced vacuum at 35°C. The product was isolated using n-Hexane and dried under vacuum to obtain the products 5a-d.

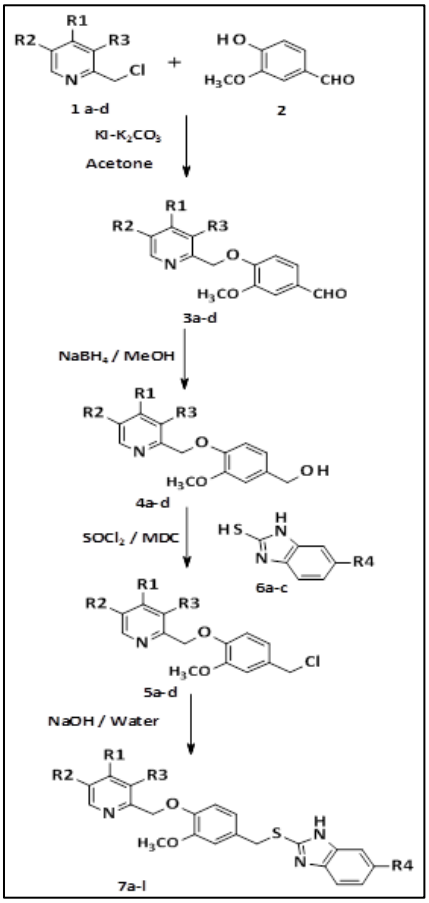
General procedure for preparation of 2-(4-((4-(2, 2, 2-trifluoroethoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxybenzylthio)-1H-benzo[d] imidazole, 7a-l

0.0242 mol of substituted 4-(2, 2, 2-trifluoroethoxy)-2-((4-(chloromethyl)-2-methoxyphenoxy) methyl)-3-methylpyridine compounds (5a-d) was charged to MDC, it contains TBAB, to this was charged a aqueous sodium hydroxide solution of (0.0242mol) substituted 2-Mercapto benzimidazole (6a-c) . The reaction mass was stirred for about 15 hours at room temperature. After the TLC complies, the material was extracted with MDC at 32±2°C and then washed with aqueous NaOH solution. The organic layer was dried with anhydrous sodium sulfate and then concentrated under vacuum at 35°C. The product was isolated using n-Hexane and dried under vacuum, to obtain 7a-l. Details of compounds synthesised with various substituents are tabulated in Table 1.

4-((4-(2, 2, 2-trifluoroethoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxybenzaldehyde, 3a

White solid with Yield: 94%; $C_{17}H_{16}F_3NO_4$: MR 137-139°C, IR (KBr, in cm $^{-1}$): 3091 (C-H, Aromatic ring), 2837 (C-H, Methoxy), 1682 (C=O, Aldehyde), 1585 (C=N, Aromatic ring), 1511 (C=C, Aromatic ring), 1135 (C-O-C), 1036 (C-F), ^{1}H NMR (DMSO-d6) δ: 2.196 (s, 3H), 3.805 (s, 3H), 4.860-4.948 (q, 2H), 5.291 (s, 2H), 7.136-7.156 (d, 1H, J = 6.0 Hz), 7.301-7.329 (d, 1H, J = 8.4 Hz), 7.393-7.399 (d, 2H, J = 1.8 Hz), 7.505-7.538 (dd, 1H), 8.334-8.354 (d, 1H, J = 6.0 Hz), 9.829 (s, 1H), ^{13}C NMR (DMSO-d6) δ: 10.30, 56.04, 64.42-65.81 (q, Due to C-F coupling), 71.28, 108.22, 110.33, 113.23, 122.06, 122.40, 126.08-126.18 (d, Due to C-F coupling), 130.40, 148.21, 149.89, 153.61, 155.13, 161.86, 191.80, ^{19}F NMR (DMSO) δ in ppm:-72.67, -72.71, -72.74, MS m/z 354.9 $[M+H]^+$

Scheme 1: The synthetic strategy for the preparation of substituted 4-[2-pyridylmethoxy] phenyl methylthio-substituted-benzimidazole (7a-l).



4-((4-methoxy-3, 5-dimethylpyridin-2-yl) methoxy)-3-methoxybenzaldehyde, 3b

White solid with 94% of Yield; $C_{17}H_{19}NO_4$:MR 137-140°C, IR (KBr, in cm $^{-1}$): 3072 (C-H, Aromatic ring), 2831 (C-H, Methoxy), 1686 (C=O, Aldehyde), 1586 (C=N, Aromatic ring), 1514 (C=C, Aromatic ring), 1146 (C-O-C), ^{1}H NMR (DMSO-d6) δ: 2.203 (s, 3H), 2.231 (s, 3H), 3.721 (s, 3H), 3.794 (s, 3H), 5.233 (s, 2H), 7.307-7.339 (d, 1H, J = 9.6 Hz), 7.382-7.386 (dd, 2H), 7.496-7.529 (d, 1H, J = 9.9 Hz), 9.818 (s, 1H), ^{13}C NMR (DMSO-d6) δ: 10.88, 13.42, 56.03, 60.23, 71.47, 110.29, 113.25, 126.24, 126.56, 126.70, 130.34, 149.13, 149.89, 153.74, 153.84, 164.09, 191.78, MS m/z 301.0 $[M+H]^+$

4-((3,4-dimethoxypyridin-2-yl) methoxy)-3-methoxybenzaldehyde, 3c

White solid with 98% of Yield; $C_{16}H_{17}NO_5$.MR 94-97°C, IR (KBr, in cm $^{-1}$): 3071 (C-H, Aromatic ring), 2839 (C-H, Methoxy), 1685 (C=O, Aldehyde), 1584 (C=N, Aromatic ring), 1512 (C=C, Aromatic ring), 1143 (C-O-C), ^{1}H NMR (DMSO-d6) δ: 3.616-3.840 (m, 6H), 3.893 (s, 3H), 5.185 (s, 2H), 7.134-7.154 (d, 1H, J = 6.0 Hz), 7.325-7.353 (d, 1H, J = 8.4 Hz), 7.382-7.388 (d, 1H, J = 1.8 Hz), 7.511-7.546 (dd, 1H), 8.203-8.220 (d, 1H, J = 5.1 Hz), 9.826 (s, 1H), ^{13}C NMR (DMSO-d6) δ: 55.98, 56.45, 61.41, 68.09, 109.58, 110.19, 112.80, 126.32, 130.25, 144.85, 146.13, 149.05, 149.73, 153.89, 158.94, 191.76, MS m/z 302.8 $[M+H]^+$

Table 1: Synthesized compounds

Compounds	R1	R2	R3	R4
1a	OCH_2CF_3	H	CH_3	-
1b	OCH_3	CH_3	CH_3	-
1c	OCH_3	H	OCH_3	-
1d	$OCH_2CH_2CH_2OCH_3$	H	CH_3	-
3a	OCH_2CF_3	H	CH_3	-
3b	OCH_3	CH_3	CH_3	-
3c	OCH_3	H	OCH_3	-
3d	$OCH_2CH_2CH_2OCH_3$	H	CH_3	-
4a	OCH_2CF_3	H	CH_3	-
4b	OCH_3	H	CH_3	-
4c	OCH_3	CH_3	OCH_3	-
4d	$OCH_2CH_2CH_2OCH_3$	H	CH_3	-
5a	OCH_2CF_3	H	CH_3	-
5b	OCH_3	H	CH_3	-
5c	OCH_3	CH_3	OCH_3	-
5d	$OCH_2CH_2CH_2OCH_3$	H	CH_3	-
6a	-	-	-	H
6b	-	-	-	OCH_3
6c	-	-	-	$OCHF_2$
7a	OCH_2CF_3	H	CH_3	H
7b	OCH_2CF_3	H	CH_3	OCH_3
7c	OCH_2CF_3	H	CH_3	$OCHF_2$
7d	OCH_3	CH_3	CH_3	H
7e	OCH_3	CH_3	CH_3	OCH_3
7f	OCH_3	CH_3	CH_3	$OCHF_2$
7g	OCH_3	H	OCH_3	H
7h	OCH_3	H	OCH_3	OCH_3
7i	OCH_3	H	OCH_3	$OCHF_2$
7j	$OCH_2CH_2CH_2OCH_3$	H	CH_3	H
7k	$OCH_2CH_2CH_2OCH_3$	H	CH_3	OCH_3
7l	$OCH_2CH_2CH_2OCH_3$	H	CH_3	$OCHF_2$

4-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxybenzaldehyde, 3d

White solid with 93% of Yield; $C_{19}H_{23}NO_5$.MR 80-84°C, IR (KBr, in cm $^{-1}$): 3071 (C-H, Aromatic ring), 2931 (C-H, Aliphatic), 2840 (C-H, Methoxy), 1681 (C=O, Aldehyde), 1584 (C=N, Aromatic ring), 1470 (C-H, Aliphatic bending) 1512 (C=C, Aromatic ring), 1128 (C-O-C), ^{1}H NMR (DMSO-d6) δ: 1.923-2.004 (p, 2H), 2.154 (s, 3H), 3.228 (s, 3H), 3.448,3.468 & 3.489 (t, 2H, J = 6.0 Hz), 3.790 (s, 3H), 4.069, 4.089 & 4.111 (t, 2H, J = 6.6 Hz), 6.974-6.991 (d, 1H, J = 5.1 Hz), 7.297-7.325 (d, 1H, J = 8.4 Hz), 7.378-7.384 (d, 1H, J = 1.8 Hz), 7.490-7.523 (dd, 1H), 8.248-8.268 (d, 1H, J = 6.0 Hz), 9.816 (s, 1H), ^{13}C NMR (DMSO-d6) δ: 10.45, 29.13, 56.01, 58.39, 65.54, 68.76, 71.48, 107.58, 110.26, 113.16, 121.92, 126.23, 130.31, 148.16, 149.80, 153.72, 154.35, 163.36, 191.75, MS m/z 345.0 $[M+H]^+$

(4-((4-(2, 2, 2-trifluoroethoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxyphenyl) methanol, 4a

White solid with95% of Yield; $C_{17}H_{18}F_3NO_4$:MR 144-146°C, IR (KBr, in cm $^{-1}$):3199 (O-H) 3100 (C-H, Aromatic ring), 2858 (C-H, Methoxy), 1587 (C=N, Aromatic ring), 1510 (C=C, Aromatic ring), 1135 (C-O-C), 1036 (C-F),^{1}H NMR (DMSO-d6) δ: 2.205 (s, 3H), 3.721 (s, 3H), 4.391-4.402 (d, 2H, J = 3.3 Hz), 4.89-7.98 (q, 2H), 5.038 (s, 1H, exchangeable with D_2O), 5.111 (s, 2H), 6.761-6.791 (dd, 1H), 6.917-6.923 (d, 1H, J = 1.8 Hz), 6.987-7.013 (d, 1H, J = 7.8 Hz), 7.112-7.132 (d, 1H, J = 6.0 Hz), 8.310-8.328 (d, 1H, J = 5.4 Hz), ^{13}C NMR (DMSO-d6) δ: 10.33, 55.90, 63.23, 64.41-65.78 (q, Due to C-F coupling), 71.60, 108.04, 111.34, 114.15, 118.95, 122.08-122.41 (d, Due to spin-spin coupling with F), 123.09, 136.23, 147.02, 148.02, 149.55, 156.03, 161.82. ^{19}F NMR (DMSO-d6) δ: -72.69, -72.72, -72.75, MS m/z 357.1 $[M+H]^+$

(4-((4-methoxy-3, 5-dimethylpyridin-2-yl) methoxy)-3-methoxyphenyl) methanol, 4b

Off white solid with 91% of yield; $C_{17}H_{21}NO_4$:MR 117-120°C, IR (KBr, in cm $^{-1}$):3283 (O-H), 3076 (C-H, Aromatic ring), 2859 (C-H, Methoxy), 1568 (C=N, Aromatic ring), 1515 (C=C, Aromatic ring), 1134 (C-O-C),^{1}H NMR (DMSO-d6) δ: 2.201 (s, 3H), 2.249 (s, 3H), 3.717 (s, 6H), 4.400 (s, 2H), 5.060 (s, 3H, exchangeable with

D_2O), 6.770-6.796 (dd, 1H), 6.917-6.921 (d, 1H, J = 1.2 Hz) , 6.998-7.024 (d, 1H, J = 7.8 Hz), 8.183 (s, 1H), ^{13}C NMR (DMSO-d6) δ: 10.92, 13.41, 55.90, 60.18, 63.23, 71.82, 111.33, 114.25, 118.97, 126.44, 126.53, 136.20, 147.11, 148.94, 149.57, 154.78, 164.02, MS m/z 303.1 $[M+H]^+$

(4-((3, 4-dimethoxypyridin-2-yl) methoxy)-3-methoxyphenyl) methanol, 4c

Off white solid with Yield: 63%; $C_{16}H_{19}NO_5$.MR 140-142°C, IR (KBr, in cm^{-1}):3178 (O-H), 3071 (C-H, Aromatic ring), 2844 (C-H, Methoxy), 1596 (C=N, Aromatic ring), 1513 (C=C, Aromatic ring), 1129 (C-O-C), ^1H NMR (DMSO-d6) δ: 3.693 (s, 3H), 3.748 (s, 3H), 3.875 (s, 3H), 4.389 (s, 2H), 5.001 (s, 3H, exchangeable with D_2O), 6.765-6.794 (dd, 1H), 6.899-6.903 (d, 1H, J = 1.2 Hz), 6.991-7.018 (d, 1H, J = 8.1 Hz), 7.103-7.121 (d, 1H, J = 5.4 Hz), 8.178-8.196 (d, 1H, J = 5.4 Hz), ^{13}C NMR (DMSO-d6) δ: 55.81, 56.34, 61.37, 63.28, 68.03, 109.28, 111.25, 113.60, 118.98, 135.91, 144.82, 145.99, 147.37, 139.34, 150.01, 158.91, MS m/z 304.7 $[M+H]^+$

(4-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxyphenyl) methanol, 4d

Off white solid with 86% of yield; $C_{19}H_{25}NO_5$.MR 90-92°C, IR (KBr, in cm^{-1}):3179 (O-H), 3035 (C-H, Aromatic ring), 2937 (C-H, Aliphatic), 1591 (C=N, Aromatic ring), 1511 (C=C, Aromatic ring), 1466 (C-H, Aliphatic bending), 1133 (C-O-C), ^1H NMR (DMSO-d6) δ: 1.928 -2.011 (p, 2H), 2.169 (s, 3H), 3.235 (s, 3H) 3.454-3.496 (t, 2H), 3.716 (s, 3H),4.072, 4.091 & 4.111 (t, 2H, J = 5.7 Hz), 4.392-4.410 (d, 2H, J = 5.4 Hz), 5.014-5.074 (m, 3H, one H, exchangeable with D_2O), 6.767-6.793 (dd, 1H), 6.917-6.921 (d, 1H, J = 1.2 Hz), 6.958-6.976 (d, 1H, J = 5.4 Hz), 6.991-7.013 (d, 1H, J = 6.6 Hz), 8.230-8.248 (d, 1H, J = 5.4 Hz),^{13}C NMR (DMSO-d6) δ: 10.48, 29.16, 55.80, 58.40, 63.25, 65.48, 68.79, 71.75, 107.40, 111.31, 114.01, 118.95, 121.88, 136.11, 147.14, 147.99, 149.51, 155.26, 163.28, MS m/z 347.0 $[M+H]^+$

4-(2, 2, 2-trifluoroethoxy)-2-((4-(chloromethyl)-2-methoxyphenoxy) methyl)-3-methylpyridine, 5a

White solid with 96% of Yield;$C_{17}H_{17}ClF_3NO_3$:MR 196-198°C, IR (KBr, in cm^{-1}): 3058 (C-H, Aromatic ring), 2831 (C-H, Methoxy), 1617 (C=N, Aromatic ring), 1515 (C=C, Aromatic ring), 1136 (C-O-C), 1035 (C-F), 827 (C-Cl), ^1H NMR (DMSO-d6) δ: 2.264 (s, 3H), 3.751 (s, 3H), 4.711 (s, 2H), 5.159-5.244 (q, 2H), 5.422 (s, 2H), 6.967-7.000 (dd, 1H), 7.108-7.114 (d, 1H, J = 1.8 Hz), 7.132-7.158 (d, 1H, J = 7.8 Hz), 7.650-7.671 (d, 1H, J = 6.3 Hz), 8.740-8.762 (d, 1H, J = 6.6 Hz), ^{13}C NMR (DMSO-d6) δ: 10.36, 39.95, 46.74, 56.14, 65.72-66.65 (q, Due to C-F coupling), 110.35, 113.63, 115.88, 121.80, 121.91, 125.53, 132.77, 142.21, 147.14, 149.92, 149.98, 167.10, ^{19}F NMR (DMSO-d6) δ: -72.53, -72.56, -72.59, MS m/z 375.1 $[M+H]^+$

2-((4-(chloromethyl)-2-methoxyphenoxy) methyl)-4-methoxy-3, 5-dimethylpyridine, 5b

Off white solid with 97% of yield; $C_{17}H_{20}ClNO_3$:MR 113-115°C, IR (KBr, in cm^{-1}):3074 (C-H, Aromatic ring), 2839 (C-H, Methoxy), 1618 (C=N, Aromatic ring), 1508 (C=C, Aromatic ring), 1134 (C-O-C), 822 (C-Cl) ^1H NMR (DMSO-d6) δ: 2.315 (s, 3H), 2.389 (s, 3H), 3.735-3.750 (d, 3H, J = 4.5 Hz), 4.024 (s, 3H), 4.705 (s, 2H), 5.431 (s, 2H), 6.956-9.689 (dd, 1H), 7.099-7.105 (d, 1H, J = 1.8 Hz) , 7.156-7.182 (d, 1H, J = 7.8 Hz), 8.617 (s, 1H),^{13}C NMR (DMSO-d6) δ: 11.30, 14.34, 46.74-61.73 (Due to C-Cl coupling), 56.01, 56.16, 66.14, 113.64, 115.96, 121.82, 123.64, 129.46, 132.73, 141.77, 147.19, 148.88, 150.01, 170.24, MS m/z 321.0 $[M+H]^+$

2-((4-(chloromethyl)-2-methoxyphenoxy) methyl)-3, 4-dimethoxypyridine, 5c

Off white solid with 97% of yield; $C_{16}H_{18}ClNO_4$.MR 146-148°C, IR (KBr, in cm^{-1}): 3049 (C-H, Aromatic ring), 2830 (C-H, Methoxy), 1614 (C=N, Aromatic ring), 1508 (C=C, Aromatic ring), 1139 (C-O-C), 729 (C-Cl), ^1H NMR (DMSO-d6) δ: 3.737 (s, 3H), 3.855 (s, 3H), 4.130 (s, 3H), 4.707 (s, 2H), 5.328 (s, 2H), 6.960-6.993 (dd, 1H), 7.090-7.097 (d, 1H, J = 2.1 Hz), 7.147-7.173 (d, 1H, J = 7.8 Hz), 7.608 (s, 1H), 8.624-8.646 (d, 1H, J = 6.6 Hz), ^{13}C NMR (DMSO-d6) δ: 46.80, 56.10, 58.63, 63.21, 63.28, 111.48, 113.57, 115.36, 121.83, 132.46, 140.17, 144.07, 145.50, 147.44, 149.77, 165.45, MS m/z 322.9 $[M+H]^+$

4-(3-methoxypropoxy)-2-((4-(chloromethyl)-2-methoxyphenoxy) methyl)-3-methylpyridine, 5d

Off white solid with 96% of yield;$C_{19}H_{24}ClNO_4$.MR 63-66°C, IR (KBr, in cm^{-1}): 3043 (C-H, Aromatic ring), 2928 (C-H, Aliphatic), 2886 (C-H, Methoxy), 1627 (C=N, Aromatic ring), 1514 (C=C, Aromatic ring), 1466 (C-H, Aliphatic bending), 1122 (C-O-C), 738 (C-Cl) ^1H NMR (DMSO-d6) δ: 1.996-2.119 (p, 2H), 2.325 (s, 3H), 3.232 (s, 3H), 3.747 (s, 3H), 3.465, 3.487 & 3.507 (t, 2H, J = 6.6 Hz), 4.373,4.395 & 4.439 (t, 3H, J = 6.6 Hz), 4.702 (s, 2H), 5.460 (s, 2H), 6.594-6.980 (dd, 1H), 7.097-7.101 (d, 1H, J = 1.2 Hz), 7.156-7.185 (d, 1H, J = 8.7 Hz), 7.595-7.617 (d, 1H, J = 6.6 Hz), 8.654-8.676 (d, 1H, J = 6.6 Hz),^{13}C NMR (DMSO-d6) δ: 10.42, 28.73, 46.24, 56.14, 58.44, 65.57, 68.38, 68.48, 109.66, 113.62, 115.81, 121.80, 121.57, 132.74, 141.50, 147.12, 148.22, 149.95, 169.30, MS m/z 365.0 $[M+H]^+$

2-(4-((4-(2,2,2-trifluoroethoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxybenzylthio)-1H-benzo[d] imidazole, 7a

Light yellow colour solid with 97% of yield; $C_{24}H_{22}F_3N_3O_3S$:MR 176-179°C, IR (KBr, in cm $^{-1}$): 3400 (N-H), 3059 (C-H, Aromatic ring), 2839 (C-H, Methoxy), 1620 (C=N, Imidazole),1588 (C=N, Aromatic ring), 1511 (C=C, Aromatic ring), 1160 (C-N, Imidazole),1133 (C-O-C), 1039 (C-F), 741 (C-S),^{1}H NMR (DMSO-d6) δ: 2.188 (s, 3H), 3.658 (s, 3H), 4.490 (s, 2H), 4.845-4.933 (q, 2H), 5.104 (s, 2H), 6.866-6.899 (dd, 1H), 6.934-6.963 (d, 1H, J = 8.7 Hz), 6.998-7.002 (d, 1H, J = 1.2 Hz), 7.035-7.055 (d, 1H, J = 6.0 Hz), 7.083-7.104 (m, 2H), 7.419-7.448 (m, 2H), 8.310-8.328 (d, 1H, J = 5.4 Hz), 12.523 (s, 1H, exchangeable with D_2O) N ^{19}F NMR (DMSO-d6) δ: -72.70, -72.73, -72.76, MS m/z 489.2$[M-H]^+$

2-(4-((4-(2,2,2-trifluoroethoxy)-3-methylpyridin-2-yl)methoxy)-3-methoxybenzylthio)-5-methoxy-1H benzo[d]imidazole, 5b

Off white solid with 90% of yield; $C_{25}H_{24}F_3N_3O_4S$:MR 181-183°C, IR (KBr, in cm $^{-1}$): 3418 (N-H), 3073 (C-H, Aromatic ring), 2831 (C-H, Methoxy), 1628 (C=N, Imidazole),1590 (C=N, Aromatic ring), 1515 (C=C, Aromatic ring), 1169 (C-N, Imidazole),1139 (C-O-C), 1034 (C-F), 744 (C-S),^{1}H NMR (DMSO-d6) δ: 2.183 (s, 3H), 3.647 (s, 3H), 3.724 (s, 3H), 4.437 (s, 2H), 4.838-4.926 (q, 2H), 5.097 (s, 2H), 6.713-6.750 (dd, 1H), 6.888-6.921 (d, 1H, J = 9.9 Hz), 6.958-6.965 (d, 1H, J = 2.1 Hz), 6.978-7.007 (d, 1H, J = 8.7 Hz), 7.033-7.039 (d, 1H, J = 1.8 Hz), 7.103-7.123 (d, 1H, J = 6.0 Hz), 7.314-7.342 (d, 1H, J = 8.4 Hz), 8.303-8.323 (d, 1H, J =6.0 Hz), ^{19}F NMR (DMSO-d6) δ: -72.70, -72.73, -72.76, MS m/z 519.2 $[M-H]^+$

2-(4-((4-(2, 2, 2-trifluoroethoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxybenzylthio)-5-(difluoromethoxy)-1H-benzo[d]imidazole, 7c

Off white solid with 93% of Yield; $C_{25}H_{22}F_5N_3O_4S$:MR 166-170°C,, IR (KBr, in cm $^{-1}$): 3419 (N-H), 3059 (C-H, Aromatic ring), 2886 (C-H, Methoxy), 1628 (C=N, Imidazole),1588 (C=N, Aromatic ring), 1513 (C=C, Aromatic ring), 1162 (C-N, Imidazole),1131 (C-O-C), 1027 (C-F), 742 (C-S),^{1}H NMR (DMSO-d6) δ: 2.190 (s, 3H), 3.667 (s, 3H), 4.485 (s, 2H), 4.845-4.933 (q, 2H), 5.106 (s, 2H), 6.892, 7.140 & 7.391 (t, 1H, Due to C-F Coupling, J = 74.4 Hz), 6.912-6.939 (dd, 1H), 6.945-6.991 (d, 1H, J = 13.8 Hz), 6.991-7.020 (d, 1H, J = 8.7 Hz), 7.072-7.077 (d, 1H, J = 1.5 Hz), 7.110-7.129 (d, 1H, J = 5.7 Hz), 7.257-7.263 (d, 1H, J = 1.8 Hz), 7.430-7.459 (d, 1H, J = 8.7 Hz), 8.310-8.328 (d, 1H, J = 5.4 Hz), ^{19}F NMR (DMSO-d6) δ: Py-F, -72.71, -72.74, -72.78, Im-F, -80.79,-81.05 MS m/z 555.2 $[M-H]^+$

2-(4-((4-methoxy-3, 5-dimethylpyridin-2-yl) methoxy)-3-methoxybenzylthio)-1H-benzo[d] imidazole, 7d

Off white solid with 98% of Yield; $C_{24}H_{25}N_3O_3S$:MR 152-155°C, IR (KBr, in cm $^{-1}$): 3425 (N-H), 305 (C-H, Aromatic ring), 2839 (C-H, Methoxy), 1618 (C=N, Imidazole),1591 (C=N, Aromatic ring), 1513 (C=C, Aromatic ring), 1163 (C-N, Imidazole),1142 (C-O-C), 1034 (C-F), 734 (C-S),^{1}H NMR(DMSO-d6) δ: 2.196 (s, 3H), 2.217 (s, 3H), 3.640 (s, 3H), 3.712 (s, 3H), 4.471 (s, 2H), 5.045 (s, 2H), 6.904-6.935 (dd, 1H), 6.991-7.021 (d, 1H, J = 9.0 Hz), 7.055-7.062 (d, 1H, J = 2.1 Hz), 7.096-7.128 (m, 2H), 7.414-7.446 (m, 2H), 8.176 (s, 1H), 12-13 (s, 1H, NH exchangeable with D_2O) , MS m/z 435.2 $[M+H]^+$

2-(4-((4-methoxy-3,5-dimethylpyridin-2-yl)methoxy)-3-methoxybenzylthio)-5-methoxy-1H-benzo[d]imidazole, 7e

Off white solid with 94% of Yield; $C_{25}H_{27}N_3O_4S$:MR 172-175°C,IR (KBr, in cm $^{-1}$): 3432 (N-H), 3087 (C-H, Aromatic ring), 2833 (C-H, Methoxy), 1628 (C=N, Imidazole),1591 (C=N, Aromatic ring), 1513 (C=C, Aromatic ring), 1158 (C-N, Imidazole),1140 (C-O-C), 740 (C-S),^{1}H NMR (DMSO-d6) δ: 2.196 (s, 3H), 2.217 (s, 3H), 3.639 (s, 3H), 3.712 (s, 3H), 3.746 (s, 3H), 4.430 (s, 2H), 5.043 (s, 2H), 6.847-6.882 (dd, 1H), 6.945 (s, 1H), 6.967-6.972 (m, 2H), 7.309-7.338 (d, 1H, J = 8.7 Hz), 8.127 (s, 1H), 12.352 (s, 1H, NH exchangeable with D_2O) , MS m/z, 465.2 $[M+H]^+$

2-(4-((4-methoxy-3, 5-dimethylpyridin-2-yl) methoxy)-3-methoxybenzylthio)-5-(difluoro methoxy)-1H-benzo[d]imidazole, 7f

Off white solid with 92% of Yield; $C25H_{25}F_2N_3O4S$:MR 181-183°C, IR (KBr, in cm $^{-1}$): 3419 (N-H), 3064 (C-H, Aromatic ring), 2833 (C-H, Methoxy), 1629 (C=N, Imidazole),1594 (C=N, Aromatic ring), 1516 (C=C, Aromatic ring), 1167 (C-N, Imidazole),1137 (C-O-C), 1037 (C-F), 748 (C-S),^{1}H NMR (DMSO-d6) δ: 2.196 (s, 3H), 2.220 (s, 3H), 3.651 (s, 3H), 3.712 (s, 3H), 4.435 (s, 2H), 5.043 (s, 2H), 6.738,6.948 & 7.238 (t, 1H,Due to C-F coupling, J = 63.0 Hz), 6.852-6.899 (m, 2H), 6.974-7.006 (m, 2H), 7.187-7.194 (d, 1H, J = 2.1 Hz), 7.370-7.399 (d, 1H, J = 8.7 Hz), 8.125 (s, 1H), ^{19}F NMR (DMSO-d6) δ: Im-F, -80.23, -80.50, MS m/z, 501.2 $[M+H]^+$

2-(4-((3, 4-dimethoxypyridin-2-yl) methoxy)-3-methoxybenzylthio)-1H-benzo[d]imidazole, 7 g

Off white solid with 87% of Yield; $C_{23}H_{23}N_3O_4S$:MR 174-176°C, IR (KBr, in cm $^{-1}$): 3425 (N-H), 3059 (C-H, Aromatic ring), 2837 (C-H, Methoxy), 1622 (C=N, Imidazole),1590 (C=N, Aromatic ring), 1510 (C=C, Aromatic ring), 1218 (C-N, Imidazole),1146 (C-O-C), 733 (C-S), ^{1}H NMR (DMSO-d6) δ: 3.630 (s, 3H), 3.729 (s, 3H), 3.874 (s, 3H), 4.740 (s, 2H), 4.994 (s, 2H), 6.906-6.941 (dd, 1H), 6.991-7.020 (d, 1H, J = 8.7 Hz), 7.046-7.053 (d, 1H, J = 2.1 Hz), 7.088-7.123 (m, 2H), 7.404-7.446 (m, 2H), 8.175-8.193 (d, 1H, J = 5.4 Hz), 11-13 (s, 1H, NH exchangeable with D_2O) , MS: [M+] at m/z 437.4

2-(4-((3, 4-dimethoxypyridin-2-yl) methoxy)-3-methoxybenzylthio)-5-methoxy-1H-benzo[d] imidazole, 7h

Off white solid with 93% of Yield; $C_{24}H_{25}N_3O_5S$:MR 164-167°C, IR (KBr, in cm^{-1}): 3419 (N-H), 3094 (C-H, Aromatic ring), 2842 (C-H, Methoxy), 1624 (C=N, Imidazole),1591 (C=N, Aromatic ring), 1513 (C=C, Aromatic ring), 1154 (C-N, Imidazole),1138 (C-O-C), 729 (C-S),^{1}H NMR (DMSO-d6) δ: 3.623 (s, 3H), 3.729 (s, 3H), 3.747 (s, 3H), 3.874 (s, 3H), 4.430 (s, 2H), 4.992 (s, 2H), 6.712-6.747 (dd, 1H), 6.884-6.917 (dd, 1H), 6.945 (d, 1H), 6.985-7.013 (d, 1H, J = 8.4 Hz), 7.103-7.123 (m, 2H), 7.305-7.334 (d, 1H, J = 8.7 Hz), 8.175-8.193 (d, 1H, J = 5.4 Hz), 11-13 (s, 1H, NH exchangeable with D_2O), MS m/z 467.4 $[M+H]^+$

2-(4-((3,4-dimethoxypyridin-2-yl)methoxy)-3-methoxybenzylthio)-5-(difluoromethoxy)-1H-benzo[d]imidazole, 7i

Off white solid with 89% of Yield; $C_{24}H_{23}F_2N_3O_5S$:MR 168-170°C, IR (KBr, in cm $^{-1}$): 3408 (N-H), 3060 (C-H, Aromatic ring), 2839 (C-H, Methoxy), 1624 (C=N, Imidazole),1591 (C=N, Aromatic ring), 1513 (C=C, Aromatic ring), 1167 (C-N, Imidazole),1129 (C-O-C), 1035 (C-F), 726 (C-S), ^{1}H NMR (DMSO-d6) δ: 3.639 (s, 3H), 3.731 (s, 3H), 3.874 (s, 3H), 4.460 (s, 2H), 4.994 (s, 2H), 6.862, 7.121 & 7.360 (t, 1H, Due to C-F Coupling, J = 77.7 Hz), 6.862-6.879 (dd, 1H), 6.870-6.879 (dd, 1H), 6.901-6.934 (d, 1H, J = 9.9 Hz), 6.934-6.987 (d, 1H, J = 15.9 Hz), 7.048-7.055 (d, 1H, J = 2.1 Hz), 7.209-7.215 (d, 1H, J = 1.8 Hz), 7.387-7.415 (d, 1H, J = 8.4 Hz), 8.175-8.193 (d, 1H, J = 5.4 Hz), ^{19}F NMR (DMSO-d6) δ:F, -80.79,-81.05, MS m/z 503.4 $[M+H]^+$

2-(4-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxybenzylthio)-1H-benzo[d]imidazole, 7j

Off white solid with 82% of Yield; $C_{26}H_{29}N_3O_4S$:MR 140-143°C, IR (KBr, in cm $^{-1}$): 3407 (N-H), 3054 (C-H, Aromatic ring), 2833 (C-H, Methoxy), 1620 (C=N, Imidazole),1591 (C=N, Aromatic ring), 1513 (C=C, Aromatic ring), 1162 (C-N, Imidazole),1140 (C-O-C), 745 (C-S),^{1}H NMR (DMSO-d6) δ: 1.883-1.966 (p, 2H), 2.091 (s, 3H), 3.187 (s, 3H), 3.416,3.436,3.458 (t, 2H, J = 6.0 Hz), 3.590 (s, 3H), 4.022,4.044,4.064 (t, 2H, J = 6.6 Hz), 4.410 (s, 2H), 5.009 (s, 2H), 6.867-6.967 (m, 3H), 6.989-6.994 (d, 1H, J = 1.5 Hz), 7.077-7.133 (m, 2H), 7.407-7.448 (m, 2H), 8.168-8.186 (d, 1H, J = 5.6 Hz), 10-14 (s, 1H, NH, exchangeable with D_2O), MS m/z 479.2 $[M+H]^+$

2-(4-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methoxy)-3-methoxybenzylthio)-5-methoxy-1H benzo[d]imidazole, 7k

Off white solid with 87% of Yield; $C_{27}H_{31}N_3O_5S$:MR 171-174°C,IR (KBr, in cm $^{-1}$): 3425 (N-H), 3090 (C-H, Aromatic ring), 2885 (C-H, Methoxy), 1627 (C=N, Imidazole),1589 (C=N, Aromatic ring), 1514 (C=C, Aromatic ring), 1156 (C-N, Imidazole),1142 (C-O-C), 744 (C-S), ^{1}H NMR (DMSO-d6) δ: 1.920-2.003 (p, 2H), 2.137 (s, 3H), 3.228 (s, 3H), 3.448,3.468,3.490 (t, 2H, J = 6.6 Hz), 3.636 (s, 3H), 3.714 (s, 2H),4.06-4.10 (t, 2H), 4.42 (s, 2H), 5.05 (s, 2H), 6.708-6.745 (dd, 1H), 6.877-6.882 (d, 1H, J = 1.5 Hz), 6.904-6.911 (d, 1H, J = 2.1 Hz), 6.943-6.977 (dd, 1H),7.006-7.018 (d, 1H, J = 3.6 Hz), 7.019-7.026 (d, 1H, J = 2.1 Hz), 7.304-7.333 (d, 1H), 8.217-8.237 (d, 1H, J = 6.0 Hz), 9-14 (s, 1H, NH, exchangeable with D_2O), MS m/z 509.2 $[M+H]^+$

2-(4-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl) methoxy)-3-methoxybenzylthio)-5-(difluoromethoxy)-1H-benzo[d]imidazole, 7l

Off white solid with 81% of Yield; $C_{27}H_{29}F_2N_3O_5S$:MR 118-122°C, IR (KBr, in cm $^{-1}$): 3426 (N-H), 3061 (C-H, Aromatic ring), 2882 (C-H, Methoxy), 1628 (C=N, Imidazole),1591 (C=N, Aromatic ring), 1514 (C=C, Aromatic ring), 1163 (C-N, Imidazole),1140 (C-O-C), 1033 (C-F), 741 (C-S),^{1}H NMR (DMSO-d6) δ: 1.922-2.003 (p, 2H), 2.139 (s, 3H), 3.448,3.470,3.490 (t, 2H, J = 6.6 Hz), 3.47 (s, 3H), 4.088 (s, 3H), 4.066,4.088,4.108 (t, 2H, J = 6.6 Hz), 4.435 (s, 2H), 5.053 (s, 2H), 6.799-6.833 (dd, 1H), 6.894-6.921 (dd, 1H), 6.955-6.999 (m, 2H), 7.057-7.062 (d, 1H, J = 1.5 Hz), 6.833, 7.072 & 7.324 (t, 1H, Due to C-F Coupling, J = 71.7 Hz), 7.160-7.167 (d, 1H, J = 2.1 Hz), 7.333-7.363 (d, 1H, J = 9.0 Hz), 8.217-8.237 (d, 1H, J = 6.0 Hz), MS m/z 545.2 $[M+H]^+$

Antimicrobial activity

Antibacterial activity by disk diffusion method: The antifungal activity studies of the novel synthesized compound (**7a-l**) have been screened using disk diffusion method. The medium used for disk diffusion procedure is Brain Heart Infusion agar. The medium was cooled to room temperature. The inoculums were prepared using a loop or swab and transfer the colonies to the plates. Turbidity was adjusted with broth to equal that of a 0.5 McFarland turbidity standard that has been vortexes within 15 minutes. Those were alternatively, standardized the suspension with a photometric device. The sterile cotton swab was dipped into the inoculums and it was rotated against the wall of the tube above the liquid to remove excess inoculums. Swab entire surface of agar plate was rotated three times approximately 60º between streaking to ensure even distribution. The aerosols were avoided by not hitting the sides of the petriplate. The inoculated plate was allowed to stand for at least 3 minutes but no longer than 15 min before making wells. The compound was added into the plate by using 5mm diameter hollow tube and heated then a pressed the inoculated, the agar plate was removed immediately by making a well in the plate. Which was made five well on each plate. Then the compound was added with concentration of 75 µl and 50 µl into the respective wells on each plate. The plate was incubated within 15 minutes. The incubated plate was monitored for 18-24 hours at 37°C in CO2 jar, confluent or nearly confluent plates was taken for reading and measured the diameter of inhibition zone to nearest millimeter by holding measuring device.

To evaluate the anti-bacterial activity of the synthesized compounds (7a-l) have been screened using disk diffusion method as described process above [14] against pathogenic organisms of three gram positive (S.Aureus, S.Mutans and E. Fecalis) and gram negative bacteria by measuring the inhibition zone in mm at 50 and 75 µg/ml concentration. Ciprofloxacin was used as the standard and was also screened under similar conditions for comparison. The results of the antibacterial studies are summarized in table 2.

Table 2: Antibacterial Activity of Synthesized Compounds (VII a - l)

Zone of inhibition in mm												
Compound	**S.Aureus (µg/ml)**			**E. Fecalis (µg/ml)**			**S.Mutans (µg/ml)**			**Klebsiella (µg/ml)**		
	50	75	CPX	50	75	CPX	50	75	CPX	50	75	CPX
VII a	R	R	R	R	15	35	R	R	35	R	R	35
VII b	R	15	25	R	R	30	R	R	R	R	R	40
VII c	R	15	25	R	R	35	R	R	R	R	R	30
VII d	R	R	25	R	R	35	12	20	35	R	R	25
VII e	R	12	20	R	10	40	15	18	35	R	R	30
VII f	R	R	20	R	R	40	10	15	35	R	R	35
VII g	18	20	25	R	R	40	R	R	35	R	R	35
VII h	R	R	R	R	R	35	R	R	R	R	R	40
VII i	R	R	R	R	R	R	R	R	R	R	8	20
VII j	R	R	R	R	R	R	R	R	R	R	R	30
VII k	20	25	30	R	R	R	R	R	R	R	R	20
VII l	R	R	30	R	R	R	R	R	R	R	R	45

Antifungal activity

Antifungal activity by disk diffusion method: The antifungal activity studies of the novel synthesized compound (**7a-l**) have been screened using disk diffusion method. The medium used for disk diffusion procedure is Sabouraud agar. The medium was cooled to room temperature. The inoculums were prepared using a loop or swab and transfer the colonies to the plates. Turbidity was adjusted with broth to equal that of a 0.5 McFarland turbidity standard that has been vortexes within 15 minutes. Those were alternatively, standardized the suspension with a photometric device. The sterile cotton swab was dipped into the inoculums and it was rotated against the wall of the tube above the liquid to remove excess inoculums. Swab entire surface of agar plate was rotated three times approximately 60º between streaking to ensure even distribution. The aerosols were avoided by not hitting the sides of the petriplate. The inoculated plate was allowed to stand for at least 3 minutes, but no longer than 15 minutes before making wells. The compound was added into the plate by using 5mm diameter hollow tube and heated then a pressed the inoculated, the agar plate was removed immediately by making a well in the plate. Which was made five well on each plate. Then the compound was added with concentration of 75 µl, 50 µl and 25 µl into the respective wells on each plate. The plate was incubated within 15 minutes. The incubated plate was monitored for 18-24 hours at 37°C in CO2 jar, confluent or nearly confluent plates was taken for reading and measured the diameter of inhibition zone to nearest millimeter by holding measuring device.

To evaluate the anti-fungal activity of compounds 7a-l, were screened using disk diffusion method as described process above [14] against three fungi A.Niger, A.Flavus and Candida by measuring the inhibition zone in mm at 25, 50 and 75 µg/ml concentration. Fluconazole was used as standard which was also screened under similar conditions for comparison. The results of the antifungal studies are summarized in table 3.

Table 3: Antifungal Activity of Synthesized Compounds (VII a-l)

Zone of inhibition in mm												
Compound	**A.Niger (µg/ml)**				**A.Flavus (µg/ml)**				**Candida (µg/ml)**			
	25	50	75	FLU	25	50	75	FLU	25	50	75	FLU
VII a	R	R	17	20	R	R	11	20	R	R	R	40
VII b	R	R	10	16	R	10	12	21	R	R	18	45
VII c	R	R	8	19	R	11	15	20	R	R	R	40
VII d	R	R	R	15	R	R	10	19	R	R	R	35
VII e	R	R	R	12	R	R	13	22	R	R	R	25
VII f	R	R	14	19	R	R	15	20	R	R	R	20
VII g	R	R	13	17	R	R	10	16	R	R	20	35
VII h	R	R	17	21	14	8	16	19	14	18	25	30
VII i	R	R	R	20	R	R	12	17	R	R	R	40
VII j	R	R	15	18	R	R	8	19	R	R	R	35
VII k	R	R	12	17	R	R	12	18	R	R	R	30
VII l	R	R	10	16	R	R	12	17	R	R	R	25

RESULTS AND DISCUSSION

The synthetic strategy for the preparation of substituted 4-[2-pyridylmethoxy] phenyl methylthio-substituted-benzimidazole (7a-l) is depicted in scheme 1. Initially condensation of substituted 2-chloromethyl pyridine (1a-d) with 4-hydroxy-3-methoxy benzaldehyde (2) in presence of KI-K_2CO_3 afforded the corresponding substituted pyridine-2-yl methoxy-3-methoxy benzaldehyde (3a-d). Reduction of these aldehydes with $NaBH_4$ in methanol produced the corresponding alcohols, which were taken to further chlorination in SO_2Cl_2 & CH_2Cl_2 to the respective substituted pyridine-2yl methoxy-3-methoxyhenyl methanol (4a-d), which were further chlorinated in SO_2Cl_2-CH_2Cl_2 to get the respective substituted pyridine-2-yl methoxy-3-methoxy benzyl chlorides (5a-d) in good yields. Finally, the required substituted 4-[2-pyridylmethoxy] phenyl methylthio-substituted-benzimidazole were synthesized by condensation between equimolar mixture of these (5a-d) and substituted 2-mercaptobenzimadazole (6a-c) as shown in scheme 1.All the compounds were isolated purified and characterized by IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and MASS spectral analysis.

The Compounds 7a–c has shown antibacterial activity about 15 mm zone of inhibition against gram positive bacteria, like E.Fecalis, S.Aureus and S.Mutans. The functional group (R1, R2 and R3) of these compounds are the same, i.e. -OCH_2CF_3, -H, -CH_3 respectively, but there is a change in the nature of R4 substituent which are respectively -H, -OCH_3 and -$OCHF_2$. Further among the R4 substituents -OCH_3 and -$OCHF_2$ had more zone of inhibition compared to -H. This may be attributed to stronger activating nature of these groups. The R4 group releases electrons, thus the sulphide part of the compound had more electron density which possibly increased the activity against bacteria.

Further in compounds 7d-f the R1, R2 and R3 functional groups are changed to -OCH_3, -CH_3, -CH_3 keeping R4 the same as -H, -OCH_3 and -$OCHF_2$. These compounds have shown antibacterial activity which is now to an extent of 20 mm zone of inhibition against gram positive bacteria like E.Fecalis, S.Aureus and S.Mutans. Further the compound 7e which has both R1 and R4, strongly activating -OCH_3 groups, showed highest activity. Thus, confirming the role of electron density on the antibacterial activity.

Among the other compounds 7k exhibited high zone of inhibition against S.Aureus bacteria, again due to the presence of strongly activating groups -$OCH_2CH_2CH_2OCH_3$, -OCH_3 in positions R1 and R4. Finally, the compounds 7a-l does not have activity against gram negative (Klebsiella) bacteria.

The Compound 7a-l has shown antifungal activity to about 8-25 mm zone of inhibition against A.Niger, A.Flavus and Candida fungi. All the compounds (7a-l) are found to have a good zone of inhibition and hence antifungal activity against A.Flavus. But the compounds 7b, 7g and 7h were better than the rest.

The Compounds 7a–c has shown antibacterial activity about 15 mm zone of inhibition against gram positive bacteria, like E.Fecalis, S.Aureus and S.Mutans. The functional group (R1, R2 and R3) of these compounds are the same, i.e. -OCH_2CF_3, -H, -CH_3 respectively, but there is a change in the nature of R4 substituent which are respectively -H,-OCH_3 and -$OCHF_2$. Further among the R4 substituents -OCH_3 and -$OCHF_2$ had more zone of

inhibition compared to -H. This may be attributed to stronger activating nature of these groups. The R4 group releases electrons, thus the sulphide part of the compound had more electron density which possibly increased the activity against bacteria.

Further in compounds 7d-f the R1, R2 and R3 functional groups are changed to $-OCH_3$, $-CH_3$, $-CH_3$ keeping R4 the same as -H, $-OCH_3$ and $-OCHF_2$. These compounds have shown antibacterial activity which is now to an extent of 20 mm zone of inhibition against gram positive bacteria like E.Fecalis, S.Aureus and S.Mutans. Further the compound 7e which has both R1 and R4, strongly activating $-OCH_3$ groups, showed highest activity. Thus, confirming the role of electron density on the antibacterial activity.

Among the other compounds 7k exhibited high zone of inhibition against S.Aureus bacteria, again due to the presence of strongly activating groups $-OCH_2CH_2CH_2OCH_3$, $-OCH_3$ in positions R1 and R4. Finally the compounds 7a-l does not have activity against gram negative (Klebsiella) bacteria.

CONCLUSION

This work describes simple reactions for the synthesis of novel biologically active heterocyclic compounds, constructed by coupling three well known drug moieties. The antibacterial activity of these compounds was evaluated against gram positive and gram negative bacteria. The target compounds, showed only moderate antibacterial and antifungal activity compared to Ciprofloxacin and Fluconazole respectively as standard drugs. The biological activity has been found to be influenced by the nature of the substituent, particularly the electron rich functionalities exhibited higher biological activity than the other.

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