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Synthesis of Novel Mutual Pro-drugs by coupling of Ibuprofen (NSAID) with Sulfa drugs

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) commonly used for the treatment of chronic inflammatory diseases suffering from several undesired side effects, the most important being gastrointestinal (GI) irritation and ulceration. The Pro-drug designing is one of the several strategies used to overcome this drawback. However, mutual pro-drug concept also can be exploited for this purpose. The mutual Pro-drug consists of two pharmacologically active agents coupled together covalently so that each acts as promoiety for the other agent and vice-versa. Since an infection always leads to inflammation. Therefore sulfa drugs can be coupled with NSAIDs as amide derivatives of NSAIDs. In this way the carrier drug (sulfonamides) may be useful to overcome some side effects of parent drug particularly gastrointestinal (GI) irritation. In this paper we wish to report simple procedure to couple Ibuprofen with various sulfa drugs to get amide derivatives. So that these mutual pro-drugs may be used for infection as well as for inflammation.

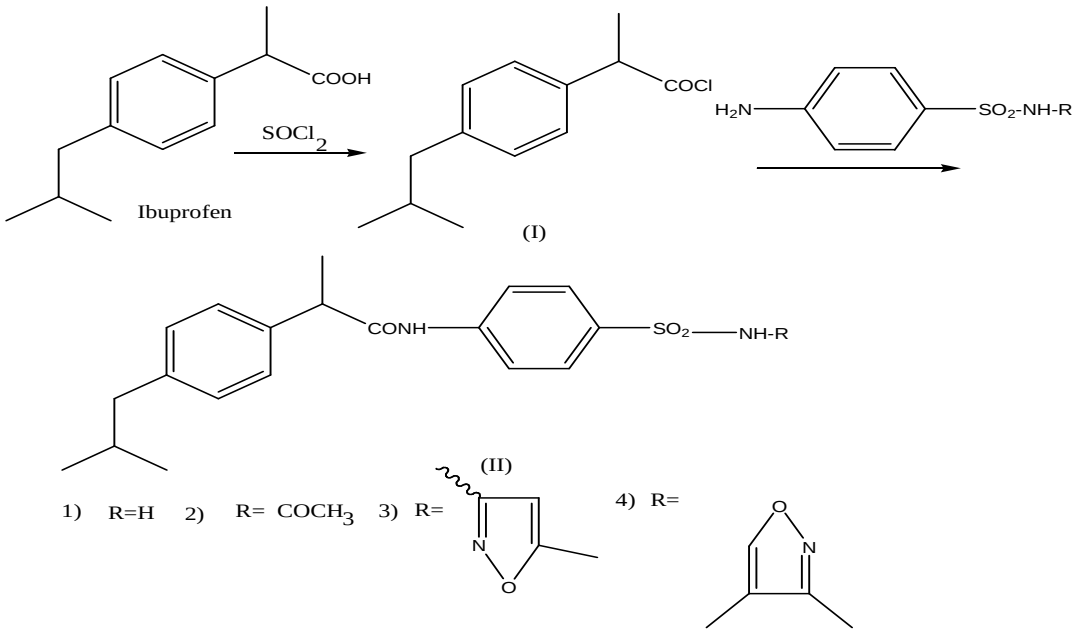
Key words: Mutual pro-drugs, Ibuprofen (NSAID), Antimicrobials Drugs (Sulfa Drugs)

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for the treatment of chronic inflammatory diseases such as arthritis. Prolonged administration of these drugs exhibits several undesired side effects, most important are gastrointestinal irritation and ulceration[1-2]

.There is enough evidence that inhibition of Cox-I rather than that of Cox-II underlies gastric ulcer formation[3].But, initial enthusiasm for selective Cox-II inhibitor as safer NSAIDs has failed due to emergence of serious cardiovascular side effect on long term use[4]. The pro-drug [5] designing is one of the several strategies used to overcome this drawback. Mutual pro-drug[6] is a type of carrier-linked, where the carrier used is another biologically active drug instead of some inert molecule. A mutual pro-drug consists of two pharmacologically active agents coupled together so that each acts as a pro-moiety for the other agent and vice versa. Mutual pro-drug design is really no different from the general drug discovery process, in which a unique substance is observed to have desirable pharmacological effects, and studies of its properties lead to the design of better drugs. It is a very fruitful area of research, and its introduction in human therapy has given successful results in improving the clinical and therapeutic effectiveness of drugs suffering from some undesirable properties that Mutual pro-drugs of ketoprofen[7], ibuprofen[8] , diclofenac[8], and flurbiprofen[9] with an antiarthritic nutraceutical D-glucosamine have been reported with reduced gastrointestinal ulcerogenicity, better analgesic/antiinflammatory effects and additional antiarthritic activity. Glucosamine is used as an antiarthritic drug and nutritional supplement in conditions like joint ache, stiffness, severely restricted movements and serious pain [10],[11]. It acts as an essential substrate for the biosynthesis of glucosaminoglycans and the hyaluronic acid backbone needed for formation of proteoglycans found in the structural matrix of joints [12]. NSAIDs are used for the symptomatic treatment of inflammation associated with arthritis but are unable to remove the underlying cause of the disease. Their prolonged use results in GI side effects. When tested in Fruend's adjuvant-induced arthritis assay, these mutual pro-drugs have shown antiarthritic activity, which was lacking in the parent drugs with comparable anti-inflammatory activity and lowered ulcerogenicity. Otherwise hinder their clinical usefulness.

Scheme-I



An infection always leads to inflammation. Therefore sulfa drugs [13] can be coupled with NSAIDs as amide derivatives of NSAIDs. In this way the carrier drug (sulfonamides) may be useful to overcome some side effects of parent drug particularly gastrointestinal (GI) irritation. In this paper we wish to report simple procedure to couple Ibuprofen with various sulfa drugs such as sulfanilide, sulfacetamide, sulfamethoxazole and sulfisoxazole to get corresponding amide derivatives. Same methodology can be applied to other NSAIDs also for temporary blockade of the free carboxylic group present in NSAIDs, till their systematic absorption. In this way these mutual pro-drugs may be used for infection as well as for inflammation. The said reaction is depicted in the scheme I.

MATERIALS AND METHODS

All reagents were purchased from Merck and used without further purification. Melting points were measured in open capillary and are uncorrected. The products were characterized by IR spectra, ^{1}H NMR and ^{13}C NMR. IR spectra were recorded on Perkin–Elmer FT-IR-1710 instrument. ^{1}H NMR was recorded on BrukerMSL-300 MHz and BrukerDRX-500 MHz instrument using TMS as an internal standard.

General Procedure for preparation of Mutual Pro-drugs.
Step 1: Preparation of Ibuprofen 2-(4-isobutylphenyl)propanoyl chloride
Step 2: Preparation of Mutual Pro Drugs by coupling the acid chloride with sulfa drug

2-(4-Isobutyl-phenyl) - propanoyl chloride (I):
Ibuprofen (2.06 g, 0.01 mol) was stirred with freshly distilled thionyl chloride (5.95 ml,0.05mol) for 8 hr. Excess thionyl chloride was removed under reduced pressure to get 2-(4-isobutyl-phenyl)-propanoyl chloride.

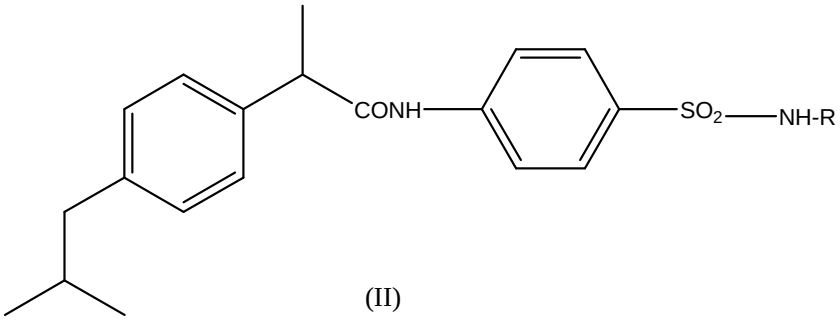
General procedure for coupling reaction of 2-(4-Isobutyl-phenyl) - propanoyl chloride (I) with sulfa drugs:
To a mixture of sulfa drug (0.01 mol) and pyridine (2.0 ml) in acetone (25.0 ml) maintained at -10°C was added with stirring a solution of 2-(4-isobutyl-phenyl)- propanoyl chloride (2.25 g, 0.01 mol) in acetone (25.0 ml) over a period of 1.0 hr. The reaction mixture was stirred for 8-10 hr and after completion of the reaction (monitored by TLC).The reaction mixture was poured into crushed ice. The residue obtained was filtered, dissolved in chloroform (100.0 ml), washed with 5% hydrochloric acid (3 × 50.0 ml), 5% sodium bicarbonate (3 × 50.0 ml) and finally with brine solution (2 × 25.0 ml). The organic layer was filtered, dried and crystallized from petroleum ether: ethyl acetate (60-80) to get Corresponding product (II).

RESULTS AND DISCUSSION

2-(4-Isobutyl-phenyl)- propanoyl chloride (I) was coupled with sulfonamide and corresponding mutual pro-drug(II) was obtained after usual workup in moderate to good yield, results are depicted in the table-1 The structure of the products where confirmed by spectral data .

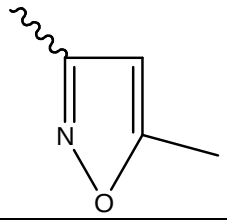
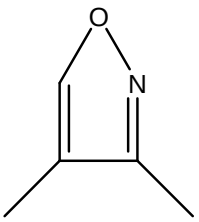
Ibuprofen containing free carboxylic group has been modified into various amide derivatives using different sulfa drug such as sulfanilide, sulfacetamide, sulfamethoxazole and sulfisoxazole

resulted in masking of the carboxylic moiety. The two component of the newly synthesized mutual pro-drugs are well known and they are in the market since decades. Therefore this mutual pro-drugs may be used to over come drawback of gastrointestinal (GI) irritation and ulceration as well as another component sulfa drug may be used against infection. However, further pharmacological studies are still required to be carried out to draw the final conclusion .



(II)

Table 1

Entry	R	Isolated Yield %	M.P.(^{0}C)
1	H	67	188
2	COCH3	47	200
3		74	176
4		72	156

SPECTRAL DATA

1) IR: KBr (NH=3331, 2900), O=C-NH (1677), C=C (1592), SO_2 (1304), ^{1}HNMR: δ =8.25(s, NH), 7.95(d, 2H), 7.45(d, 2H), 7.2(d, 2H), 7.15(d, 2H), 3.65(q, 1H), 2.35(d, 2H), 2.0(s, NH), 1.85(m, 1H), 1.6(d, 3H), 0.95(d, 6H), ^{13}C-NMR: δ= C=O(172.97), Ar C (142.08, 139.96, 138.46, 137.47), ArCH(129.05, 126.96, 126.71, 119.00,) , CH(44.78, 46.55), CH_2(44.78) , CH_3(22.22, 18.68, 30.14)

2) IR: KBr NH (2923, 2854) C=C(1591, 1461), SO_2(1377), ^{1}HNMR: δ = 7.85(2H, d), 7.5(2H, d), 7.15(2H, d), 7.1(2H, d), 4.65(s, NH,), 3.65(1H, q), 2.35(2H, d), 1.85(1H, m), 1.61(d, 3H,), 1.6(s, 3H), 1.2(s, NH), 0.95(6H, d), ^{13}C-NMR: δ C=0(173.39, 168.73), Ar C(143.61, 140.11,

138.19, 132.68), ArCH(132.08, 128.79, 126.79, 118.60), CH(44.60, 29.80,), CH_2(46.48), CH_3(23.10, 22.5, 18.52).

3) IR NH(2924,2854), C=O(1702),C=C (1460), SO_2(1377), ^{1}HNMR: δ =8.55(s, NH), 7.65(d , 2H), 7.5(d, 2H), 7.20(d, 2H), 7.15(2H, d), 6.25(s, NH), 6.25(s, 1H), 3.85(q, 1H), 2.45(d , 2H), 2.25(s, 3H), 1.95(m, 1H), 1.55(d, 3H), 0.95(d, 6H), ^{13}C-NMR: δ C=O(173.58), C=C(95.00, 171, 158), ArC(142.65, 141.07, 137.51, 133.21), ArCH(129.70, 128.14, 127.17, 119.39), CH_2(47.47), $2CH_3$(22.26, 18.49, 12.62), CH(30.06, 42.87).

4) IR : NH (2925,2725) , O=C-NH(1677), C=C (1593), SO_2(1374), ^{1}HNMR: δ=9.25(s, 1NH), 7.85(d, 2H), 7.75(d, 2H), 7.50(d, 2H), 7.25(d, 2H), 6.2(s, NH), 3.65(q, 1H), 2.35(s, 6H), 2.45(d, 2H), 1.45(d, 3H), 1.95(m, 1H), 0.95(d, 6H), ^{13}C-NMR: δ C=O(174.21), C(172.93, 169.08, 157.49, 143.19, 139.17, 138.31, 133.14), ArCH(126.70, 128.88, 127.64, 118.83), CH_3(22.10, 18.82, 18.50, 12.12), CH_2(46.36), CH(44.66, 29.79).

CONCLUSION

A very simple strategy is developed to synthesize mutual pro-drugs which is avoiding the side effect of gastrointestinal irritation of NSAIDs and the carrier drug maintain the corresponding microbial activity also. Such type of coupling is possible with other NSAIDs also.

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