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Synthesis and biological evaluation of some 5-ethoxycarbonyl-6-isopropylamino-4-(substitutedphenyl)aminopyrimidines as potent analgesic and anti-inflammatory agents

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Abstract—Synthesis and biological evaluation of some 5-ethoxycarbonyl-6-isopropylamino-4-(substitutedphenyl)aminopyrimidines have been achieved by cyclization of *N*-[2-ethoxycarbonyl-2-cyano-1-(isopropylamino)vinyl] formamidine in presence of dry HCl in dioxane followed by nucleophilic substitution of 4-chloro group with substituted aromatic amine or phenoxide. Target compounds were evaluated for their analgesic and anti-inflammatory potential by known experimental models. Some of the compounds emerged out as more potent than standard drugs. Very low ulcer index was observed for the potent compounds.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of pain and inflammation. Most currently used NSAIDs have limitations for therapeutic use since they cause gastrointestinal and renal side effects, which are inseparable from their pharmacological activities. These compounds non-selectively inhibit the two isoforms of the cyclooxygenase (COX-1 and COX-2) and thus prevent the metabolism of cellular arachidonic acid (AA) and the upregulation of prostaglandin formation, which otherwise lead to an increase of vascular permeability, edema, hyperalgesia, pyrexia, and inflammation. Therefore, the synthesis of new molecules devoid of these toxicities has been of prime interest for medicinal chemists in recent years. In addition to COX, the 5- lipoxygenase (5-LO) enzyme is another key enzyme which is involved in the AA cascade. Leukotrienes, produced through the 5-LO enzyme pathway, may also contribute to both inflammation and NSAID-induced side effects. For these reasons, compounds that are dual inhibitors of both COX and 5-LO are being studied as potential analgesic and anti-inflammatory agents with an improved safety profile in comparison to NSAIDs.[1,2] Currently, various chemical families of dual COX/5-LO inhibitors can be found in the scientific literatures.[3]

In continuation of our work to get potent and safe pyrimidine NSAID, some 5-ethoxycarbonyl-6-isopropylamino-4-(substitutedphenyl)aminopyrimidines have been designed. Earlier work from our laboratory suggested that isopropylamino group at C-6 and ethoxycarbonyl group at C-5 position are essential for potent analgesic and anti-inflammatory activity. As most of the NSAIDs contain aryl ring, it was thought of interest to incorporate aryl group at C-4 position through imino (–NH) or ethereal(–O–) linkage. Starting material was synthesized as per Scheme 1. Target compounds were synthesized by cyclization of *N*-[2-ethoxycarbonyl-2-cyano-1-(isopropylamino)vinyl] formamidine[4] in presence of dry HCl in dioxane to afford 5-ethoxycarbonyl-4-chloro-6-isopropylaminopyrimidines[5,6] (Table 1).

Nucleophilic substitution[7] of 4-chloro group by aromatic amine[8] or phenoxide[9] provided target compounds (Scheme 2).

All compounds were tested for analgesic activity using model—inhibition in acetic acid-induced writhings in

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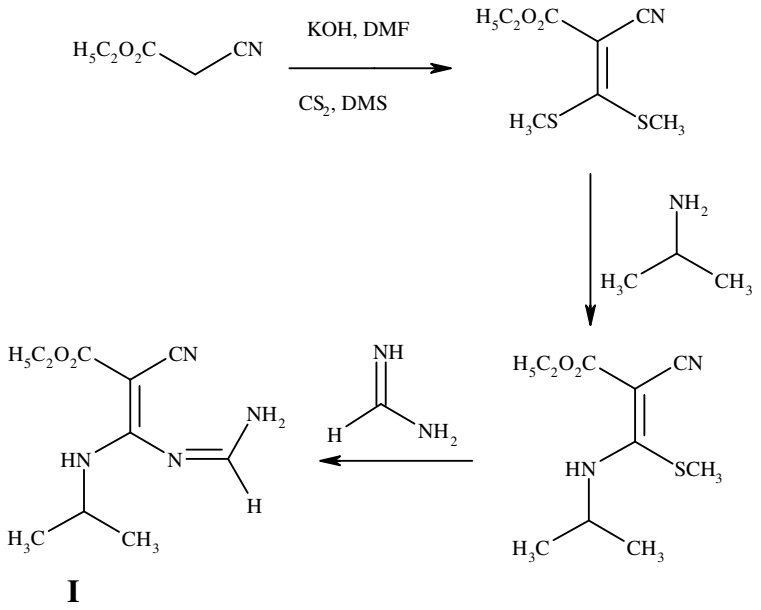
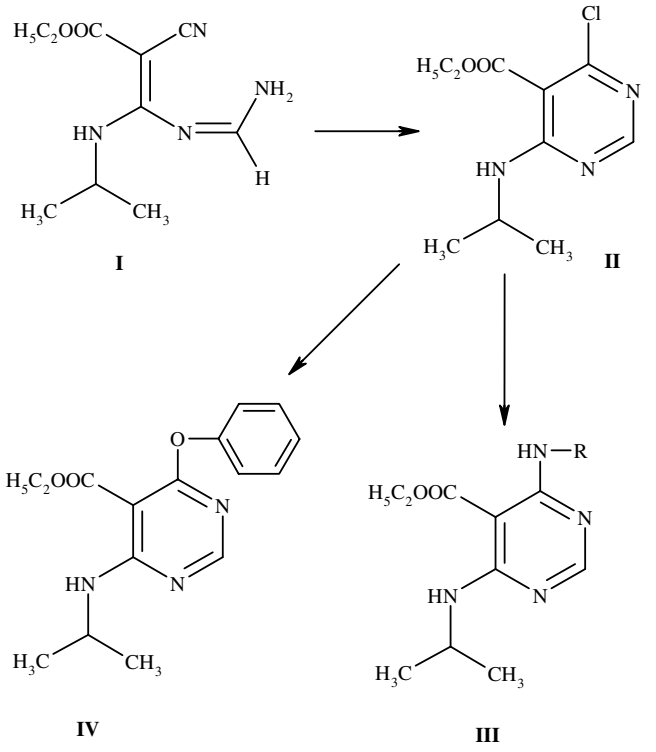


Scheme 1.

Table 1. Physical data of 5-ethoxycarbonyl-6-isopropylamino-4-(substitutedphenyl)aminopyrimidines (**IIIa**–**IIIe**, **IV**)

Compound	R[a]	Melting point (°C)	% Yield	Molecular formula
IIIa	*p*-Cl–C_6H_4	112–114	72.9	$C_{16}H_{19}ClN_4O_2$
IIIb	*p*-NO_2–C_6H_4	135–138	78.0	$C_{16}H_{19}N_5O_4$
IIIc	*p*-CH_3–C_6H_4	145–148	62.2	$C_{17}H_{22}N_4O_2$
IIId	*p*-OCH_3–C_6H_4	75–78	55.5	$C_{17}H_{22}N_4O_3$
IIIe	*p*-SO_2NH_2–C_6H_4	149–154	61.2	$C_{16}H_{21}N_5O_4S$
IV	–OC_6H_5	60–64	87.5	$C_{16}H_{19}N_3O_3$

[a] Solvent for recrystallization: methanol.



Scheme 2.

albino mice.[10] Statistically significant results were obtained with compound **IIId**, being more potent than diclofenac sodium. Acute anti-inflammatory activity was determined using known experimental models.[11] Ulcerogenic potential of the potent compounds was also evaluated.[12] Significant anti-inflammatory activity with very low ulcer index was observed with compounds **IIIc** and **IIIe** (Table 2).

In summary, compounds with potent analgesic and anti-inflammatory activities with very low ulcerogenic poten-

Table 2. Analgesic activity, anti-inflammatory activity and ulcerogenic potential of 5-ethoxycarbonyl-6-isopropylamino-4-(substitutedphenyl) aminopyrimidines

Compound	% Inhibition of writhing[a]	% Inhibition of inflammation ± SEM[a]	Ulcer Index ± SEM[a]
IIIa	70.23	30.85 ± 3.58	—
IIIb	77.38	84.56 ± 0.61	—
IIIc	72.02	89.69 ± 0.03	0.290 ± 0.024
IIId	85.11	62.72 ± 4.57	—
IIIe	72.61	87.65 ± 3.26	0.241 ± 0.104
IV	70.23	55.50 ± 3.20	—
Diclofenac sodium	77.98	—	0.805 ± 0.120
Celecoxib	—	82.09 ± 4.31	0.104 ± 0.005

[a] $n = 5$, dose = 50 mg/kg po.

tial are reported in the present study. Compounds **IIIb**, **IIIc**, and **IIIe** showed potent anti-inflammatory activity with very low ulcerogenic potential when compared with that of the standard drugs celecoxib and diclofenac sodium, respectively. However, ulcerogenic potential was remarkably more than celecoxib. Compound **IIId** exhibited greater analgesic activity than the reference standard diclofenac sodium. This series opened new doors for possible modifications of the pharmacophoric requirements of NSAIDs and future exploitations.

References and notes

1. Charlier, C.; Michaux, C. *Eur. J. Med. Chem.* **2003**, *38*, 645.
2. Unangst, P. C.; Connor, D. T.; Centenko, W. A.; Sorenson, R. J.; Kostlan, R. K.; Sircar, J. C.; Wright, C. D.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1994**, *37*, 322.
3. de Leval, X.; Delarge, J. J.; Pirotte, B.; Dogne, J. M. *Curr. Med. Chem.* **2002**, *9*, 941.
4. Shishoo, C. J.; Chhabria, M. T.; Gandhi, T. P.; Bangaru, R. A. *Arzneim.-Forsch./Drug Res.* **1997**, *47*, 35.
5. Chhabria, M. T. Ph. D. Thesis, Gujarat University, India, May 1998.
6. Chhabria, M. T.; Shishoo, C. J. *Heterocycles* **1999**, *51*, 2723.
7. Taylor, E. C.; Gillespie, P. *J. Org. Chem.* **1992**, *57*, 5757.
8. General synthetic procedure and analytical data for **II**, **IIIa**–**IIIe**: To *N*-[2-ethoxycarbonyl-2-cyano-1-(isopropylamino)vinyl]formamidine (0.01 mol), dioxane (30 ml) saturated with dry hydrogen chloride gas was added and stirred for 3 h. The reaction mixture was allowed to stand at room temperature for 12 h and poured into ice. The solid obtained was filtered, triturated with saturated sodium bicarbonate solution, filtered, washed with water, and dried. Crystallization of the crude product from *n*-hexane afforded colorless crystalline product **II**. Compound **II**: ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.9–1.8 (m, 10 H, –NH–CH(CH_3)$_2$, COOCH$_2$CH_3, –NH–CH(CH$_3$)$_2$), 4.3–4.5 (q, 2H, COOCH_2CH$_3$), 8.12 (s, 1H, –NH–CH(CH$_3$)$_2$; D_2O exchangeable), 8.47 (s, 1H, ^{2}C–H); LC-MS *m*/*z* 244.4 (M^+, $C_{10}H_{14}ClN_3O_2$, required 243.67); A mixture of **II** (0.01 mol), substituted amine (0.01 mol), and catalytic amount of concentrated HCl in isopropylalcohol (15 ml) was refluxed for 3 h. The reaction mixture was allowed to cool to room temperature and poured into ice. The crude solid product so obtained was filtered, washed with excess of water, and dried. Recrystallization of crude product from methanol yielded colorless crystalline product in good yields (60–90%). Compound **IIIa**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21–1.27 (m, 6H, –NH–CH(CH_3)$_2$), 1.45–1.49 (t, 3H, –COOCH$_2$CH_3), 4.3–4.4 (m, 1H, –NH–CH(CH$_3$)$_2$), 4.41–4.45 (q, 2H, –COOCH_2CH$_3$), 7.2–7.3 (d, 2H, Ar-2′,6′-*H*), 7.50–7.53 (d, 2H, Ar-3′,5′-*H*), 7.92–7.93 (d, 1H, –NH–CH(CH$_3$)$_2$; D_2O exchangeable), 8.21 (s, 1H, ^{2}C–H), 10.26 (s, 1H, –NH–C_6H_4; D_2O exchangeable); LC-MS *m*/*z* 334.8 (M^+), 336.8 (M+2) ($C_{16}H_{19}ClN_4O_2$, required 333.81). Compound **IIIb**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25–1.28 (m, 6H, –NH–CH(CH_3)$_2$), 1.48–1.51 (t, 3H, –COOCH$_2$CH_3), 4.37–4.42 (m, 1H, –NH–CH(CH$_3$)$_2$), 4.43–4.49 (q, 2H, –COOCH_2CH$_3$), 7.86–7.91 (d, 2H, Ar-2′,6′-*H*), 7.97–7.99 (d, 2H, Ar-3′,5′-*H*), 8.16–8.18 (d, 1H, –NH–CH(CH$_3$)$_2$; D_2O exchangeable), 8.27 (s, 1H, ^{2}C–H), 10.88 (s, 1H, –NH–C_6H_4; D_2O exchangeable); LC-MS *m*/*z* 346.2 (M^+, $C_{16}H_{19}N_5O_4$, required 345.36). Compound **IIIc**: ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.5–1.7 (m, 10H, –NH–CH(CH_3)$_2$, COOCH$_2$CH_3, –NH–CH(CH$_3$)$_2$), 2.37 (s, 3H, *p*-CH_3–C_6H_4), 4.4–4.6 (q, 2H, COOCH_2CH$_3$), 7.1–7.4 (m, 4H, *p*-CH$_3$–C_6H_4), 8.20 (s, 1H, –NH–CH(CH$_3$)$_2$; D_2O exchangeable), 8.47 (s, 1H, ^{2}C–H), 10.51 (s, 1H, –NH–C_6H_4; D_2O exchangeable); LC-MS *m*/*z* 315.0 (M^+, $C_{17}H_{22}N_4O_2$, required 314.39). Compound **IIId**: ^{1}H NMR (60 MHz, $CDCl_3$): 0.8–1.5 (m, 10H, –NH–CH(CH_3)$_2$, COOCH$_2$CH_3, –NH–CH(CH$_3$)$_2$), 2.67 (s, 3H, *p*-OCH_3–C_6H_4), 4.3–4.5 (q, 2H, COOCH_2CH$_3$), 7.3–7.5 (m, 4H, *p*-OCH$_3$–C_6H_4), 7.97 (s, 1H, –NH–CH(CH$_3$)$_2$; D_2O exchangeable), 8.17 (s, 1H, ^{2}C–H), 9.96 (s, 1H, –NH–C_6H_4; D_2O exchangeable); LC-MS *m*/*z* 331.0 (M^+, $C_{17}H_{22}N_4O_3$, required 330.39). Compound **IIIe**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25–1.27 (m, 6H, –NH–CH(CH_3)$_2$), 1.47–1.50 (t, 3H, –COOCH$_2$CH_3), 4.36–4.40 (m, 1H, –NH–CH(CH$_3$)$_2$), 4.43–4.47 (q, 2H, –COOCH_2CH$_3$), 5.16 (s, 2H, –NH–C_6H_4– SO_2NH_2, D_2O exchangeable), 7.74–7.77 (d, 2H, Ar-2′,6′-*H*), 7.82–7.85 (d, 2H, Ar-3′,5′-*H*), 7.90–7.91 (s, 1H, –NH–CH(CH$_3$)$_2$; D_2O exchangeable), 8.24 (s, 1H, ^{2}C–H), 10.61 (s, 1H, –NH–C_6H_4; D_2O exchangeable); LC-MS *m*/*z* 380.2 (M^+, $C_{16}H_{21}N_5O_4S$, required 379.44).
9. Synthetic procedure and analytical data for **IV**: A mixture of **II** (0.01 mol) and potassium phenoxide (0.01 mol) in dimethylformamide (15 ml) was refluxed for 3 h. The reaction mixture was allowed to cool to room temperature and poured into ice. The solid so obtained was filtered, washed with excess of water, and dried. Crystallization of crude product from methanol yielded colorless crystalline product (87.5% yield). ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.2–1.4 (m, 10H, –NH–CH(CH_3)$_2$, COOCH$_2$CH_3, –NH–CH(CH$_3$)$_2$), 4.3–4.5 (q, 2H, COOCH_2CH$_3$), 7.0–7.5 (m, 5H, –OC_6H_5), 8.20 (s, 1H, –NH–CH(CH$_3$)$_2$; D_2O exchangeable), 8.40 (s, 1H, ^{2}C–H); LC-MS *m*/*z* 302.0 (M^+, $C_{16}H_{19}N_3O_3$, required 301.35).
10. Greenhouse, D. D. *J. Pharm. Exp. Ther.* **1969**, *169*, 29.
11. Winter, C. A.; Risley, E. A.; Nuss, G. W. *Proc. Soc. Expt. Biol. Med.* **1962**, *111*, 544.
12. Scibert, K.; Zhang, Y. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 12013.