An Efficient Biginelli One-Pot Synthesis of New Benzoxazole-Substituted Dihydropyrimidinones and Thiones Catalysed by Alumina-Supported Trifluoromethane Sulfonic Acid Under Solvent Free Conditions

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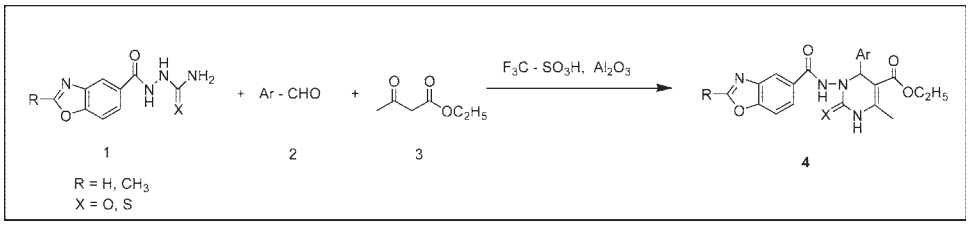

An efficient synthesis of benzoxazole-substituted 3,4-dihydropyrimidinones (DHPMs) using alumina supported trifluoromethane sulfonic acid as the catalyst for the first time from an aldehyde, β-keto ester, and benzoxazole-substituted urea and thiourea under solvent-free conditions is described. When compared with the classical Biginelli reaction conditions, this new method consistently has the advantage of excellent yields (80–93%) and short reaction time (30–120 minutes) at 120°C temperature.

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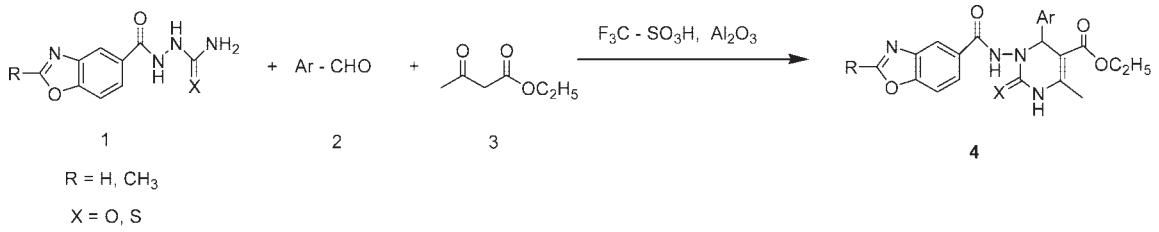
INTRODUCTION

The Biginelli (1893) reaction [1] is a simple one-pot condensation of an aldehyde, keto ester, and urea or thiourea in the presence of catalytic amount of acid to produce 3,4-dihydropyrimidin-2(1*H*)-ones. Dihydropyrimidinones (DHPMs) and their derivatives exhibit wide range of biological activities such as antibacterial, antiviral, antitumour, and anti-inflamatory actions [2]. Biginelli compounds exhibit pharmacological activities as calcium channel blockers, antihypertensive agents, α - 1a–antagonists, and neuro peptide Y(NPY) antagonists [3–6]. Biological activities of some marine alkaloids isolated were also found to contain the dihydropyrimidinone-5-carboxylate core [7]. Most notably among them are batezelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors [8–10]. Consequently, syntheses of Biginelli compounds have gained importance, which often suffer from low yields practically in case of substituted aromatic and aliphatic aldehydes [11–13]. Even though, high yields could be achieved by following complex multistep procedures [14–17], these methods lack the simplicity of original one-pot Biginelli protocol. Therefore, Biginelli reaction continues to attract the attention of researchers for the discovery of a milder and efficient procedure for the synthesis of dihydropyrimidinones.

Similarly, benzoxazole nucleus can also be frequently recognized in the structure of numerous naturally occurring compounds with interesting biological and pharmacological properties. Benzaxazoles have been found to possess marked biological effects as anti inflammatory [18,19], anticancer [20] and antimicrobial [21,22] agents. In view of this benzoxazole-substituted urea and thiourea are used in the synthesis of 3,4-dihydropyrimidinones to get more biodynamic compounds.

In recent years, several synthetic procedures for preparing of DHPMs have been reported including classical conditions with microwave irradiation [23,24] and by using Lewis acids as well as protic acids as promoters such as [25–30] Conc. HCl, $BF_3.OEt_2$, PPE, KSF clay, $InCl_3$, $LaCl_3$, lanthanide triflate, H_2SO_4, ceric ammonium nitrate (CAN), $Mn(OAc)_3$, ion-exchange resin, 1*n*-butyl-3-methyl imidazolium tetra fluoroborate (BMImBF4), $BiCl_3$, $LiClO_4$, $InBr_3$, $FeCl_3$, $ZrCl_4$, $Cu(OTf)_2$, $Bi(OTf)_3$, LiBr, ytterbium triflates, NH_4Cl, $MgBr_2$, $SiO_2/NaHSO_4$, $CdCl_2$, and other reagents [31] have been found to be effective. Many of these methods involve expensive reagents, stochiometric amounts of catalysts, strongly acidic conditions, long reaction times, unsatisfactory yields, and incompatibility with other functional groups. Therefore, the development of a neutral alternative would extend the scope of the Biginelli reaction.

Scheme 1



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Recently, the use of solid supported reagents [32] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup, and recoverability of catalysts. Among the various heterogeneous catalysts, particularly, alumina supported trifluoromethane sulfonic acid has advantages of low cost, ease of preparation, and catalyst recycling. As the reaction is heterogeneous in nature, the catalyst can conveniently be separated by simple filtration. In view of the recent surge in the use of heterogeneous catalysts [33–35], we wish to report a simple, convenient, and efficient method for the preparation of benzoxazole-substituted dihydropyrimidinone derivatives using alumina [36] supported trifluoromethane sulfonic acid, as an inexpensive and eco-friendly catalyst. This catalyst can act as eco-friendly for a variety of organic transformations because it is nonvolatile, recyclable, inexplosive, easy to handle, and thermally robust. In view of the emerging importance of heterogeneous catalysts, we wish to explore the use of alumina supported trifluoromethane sulfonic acid [37] as recyclable catalyst in the synthesis of DHPMs using substituted urea and thiourea.

RESULTS AND DISCUSSION

Initially, we have studied the Bignelli's one-pot condensation reaction of benzaldehyde (1.0 mmol) with benzoxazole-substituted urea (1.2 mmol) and ethyl acetoacetate (1.2 mmol) using 5 mol % of alumina-supported trifluoromethane sulfonic acid as catalyst under solvent free conditions (Scheme 1). The reaction is very fast and 90% conversion was observed in 1 h.

Encouraged by these results, we examined several aromatic and aliphatic aldehydes under optimized conditions (Table 1). Furthermore, the use of just 5 mol % alumina-supported trifluoromethane sulfonic acid as catalyst is sufficient to promote the reaction. There are no improvements in the reaction rates and yields by increasing the amount of the catalyst from 5 to 10 mol %. The best results were achieved when the reactions were carried out at 120°C temperature in an oil bath for 30–120 minutes in the presence of catalytic amount of alumina supported trifluoromethane sulfonic acid catalyst. The results are listed in Table 1. Another important feature of this procedure is the stability of a variety of functional groups such as ether, hydroxy, halides, nitro, *etc*., under these reaction conditions.

Benzoxazole-substituted urea and thiourea has been used with similar success to provide the corresponding dihydropyrimidinones and thiones in high yields, which are also of much interest with regard to biological activity. An acid sensitive aldehyde, worked well without formation of any side product. It is noteworthy which the survival of a variety of functional groups such as ether, hydroxy, halides, nitro, unsaturation, *etc*, under the reaction conditions.

The efficiency of the recovered catalyst was verified with the reaction of benzaldehyde, benzoxazole -substituted urea and ethyl acetoacetate (Entry 1). Using fresh catalyst, the yield of product (4**a**) was 90% while the recovered catalyst in the three subsequent recyclization the yields were 89, 87, and 86.

CONCLUSION

In summary, we have developed a new methodology for the synthesis of substituted DHPMs by using substituted urea and thiourea in the presence of a catalytic amount of alumina supported trifluoromethane sulfonic acid at 120°C temperature. Thus, alumina-supported trifluoromethane sulfonic acid mediated one-pot synthesis of DHPMs is, therefore, a simple, high yielding, time saving, and eco-friendly process. The catalyst can be prepared from available inexpensive reagents and can be easy recycled, which is heterogeneous and nonhazardous.

EXPERIMENTAL

All chemicals were A. R. grade obtained from Qualigens, India. All the solvents were purified by standard techniques. Column chromatographic separations were carried out on Silicagel 100–200 mesh size. I.R Spectra were scanned on a Perkin-Elmer, 1310 Spectrophotometer with sodium chloride optics. NMR spectra were recorded on a varian FT-200 MHz

Table 1

Alumina-supported trifluoromethane sulfonic acid-catalyzed synthesis of dihydropyrimidinones and thio derivatives.

Entry	R	Ar	X	Products	Time (min)	M.P. (°C)	Yield (%)
1	H	C_6H_5	O	**4a**	30	171–173	90
2	CH_3	C_6H_5	O	**4b**	60	164–165	87
3	H	4-ClC_6H_4	O	**4c**	40	193–194	90
4	CH_3	4-ClC_6H_4	O	**4d**	70	201–203	88
5	H	4-$NO_2C_6H_5$	O	**4e**	40	196–198	91
6	CH_3	4-$NO_2C_6H_4$	O	**4f**	80	209–210	87
7	H	4-$(CH_3)_2NC_6H_4$	O	**4g**	60	183–185	88
8	CH_3	4-$(CH_3)_2NC_6H_4$	O	**4h**	120	188–190	84
9	H	2-OHC_6H_4	O	**4i**	40	151–153	93
10	CH_3	2-OHC_6H_4	O	**4j**	60	167–168	86
11	H	Furyl	O	**4k**	50	217–219	82
12	CH_3	Furyl	O	**4l**	70	213–214	80
13	H	C_6H_5	S	**4m**	40	178–180	88
14	CH_3	C_6H_5	S	**4n**	70	161–163	85
15	H	4-ClC_6H_4	S	**4o**	60	199–200	87
16	CH_3	4-ClC_6H_4	S	**4p**	70	191–192	84
17	H	4-$NO_2C_6H_4$	S	**4q**	60	204–206	90
18	CH_3	4-$NO_2C_6H_4$	S	**4r**	80	211–212	88
19	H	4-$(CH_3)_2NC_6H_4$	S	**4s**	90	181–182	80
20	CH_3	4-$(CH_3)_2NC_6H_4$	S	**4t**	120	186–187	87
21	H	2-OHC_6H_4	S	**4u**	60	147–149	90
22	CH_3	2-OHC_6H_4	S	**4v**	90	156–158	82
23	H	Furyl	S	**4w**	80	207–208	83
24	CH_3	Furyl	S	**4x**	120	219–221	85

(GEMINI) using tetramethyl silane (TMS) as the internal standard. Mass spectra were obtained on micro Mass VG70-70H spectrometer operating at 70 eV using a direct inlet system.

Preparation of the catalyst. The catalyst was prepared by mixing alumina (5 mmol) with a trifluoromethane sulfonic acid (5 mmol) in distilled water (10 mL). The resulting mixture was stirred for 30 minutes to absorb triflouromethane sulfonic acid on the surface of alumina. After removal of water in a rotary evaporator, the solid powder was dried at 120°C for 2–3 h under reduced pressure. The drying temperature was maintained below the decomposition temperatures of the salts.

General procedure for the synthesis of DHPMs. A solution of an appropriate β-keto ester (1.2 mmol), corresponding aldehyde (1.0 mmol), benzaxazole substituted urea or thiourea (1.2 mmol), and alumina-supported trifluoromethane sulfonic acid (5 mol %) under solvent-free conditions was heated at 120°C (completion of reaction was monitored by TLC). The reaction mixture was washed thoroughly with water, filtered and recrystallized from methanol to afford pure product. The spectral data of the compounds are given below.

Entry 1 (4a). Solid, m.p. 171–173°C, ^{1}H NMR ($CDCl_3$): δ 1.20 (*t*, 3H, *J* = 7.0 Hz), 2.30 (*s*, 3H), 4.10 (*q*, 2H, *J* = 7.0 Hz), 4.72 (*s*, 1H), 6.72–8.94 (*m*, 9H, Ar—H), 9.64 (bs, 1H, NH), 10.48 (bs, 1H, NH). EMS: *m*/*z*: 420(M^+). IR (KBr): ν = 3427, 1715, 1686, 1608, 1584. Anal. Calc. for $C_{22}H_{20}N_4O_5$ (420.14): C, 62.85; H, 4.79; N, 13.33. Found: C, 62.83; H, 4.76; N, 13.32.

Entry 2 (4b). Solid, m.p. 164–165°C, ^{1}H NMR ($CDCl_3$): δ 1.22 (*t*, 3H, *J* = 7.0 Hz), 2.34 (*s*, 3H), 2.51(*s*, 3H), 4.16 (*q*, 2H, *J* = 7.0 Hz), 4.76 (*s*, 1H), 6.64–8.73 (*m*, 8H, Ar—H), 9.46 (bs, 1H, NH), 10.24 (bs, 1H, NH). EMS: *m*/*z*: 434(M^+). IR (KBr): ν = 3345, 1721, 1682, 1610, 1589. Anal. Calc. for $C_{23}H_{22}N_4O_5$ (434.16): C, 63.59; H, 5.10; N, 12.90. Found: C, 63.57; H, 5.06; N, 12.80.

Entry 3 (4c). Solid, m.p. 193–194°C, ^{1}H NMR ($CDCl_3$): δ 1.24 (*t*, 3H, *J* = 7.0 Hz), 2.38 (*s*, 3H), 4.20 (*q*, 2H, J = 7.0 Hz), 4.84 (*s*, 1H), 6.84–8.89 (*m*, 8H, Ar—H), 9.42 (bs, 1H, NH), 10.12 (bs, 1H, NH). EMS: *m*/*z*: 454(M^+). IR (KBr): ν = 3340, 1725, 1695, 1612, 1578. Anal. Calc. for $C_{22}H_{19}ClN_4O_5$ (454.1): C, 58.09; H, 4.21; N, 12.32; Cl, 7.79;. Found: C, 58.03; H, 4.18; N, 12.30; Cl, 7.70.

Entry 4 (4d). Solid, m.p. 201–203°C, ^{1}H NMR ($CDCl_3$): δ 1.19 (*t*, 3H, *J* = 7.0 Hz), 2.36 (*s*, 3H), 2.56(*s*, 3H), 4.18 (*q*, 2H, *J* = 7.0 Hz), 4.83 (*s*, 1H), 6.78–8.74 (m, 7H, Ar—H), 9.24 (bs, 1H, NH), 10.76 (bs, 1H, NH). EMS: *m*/*z*: 468(M^+). IR (KBr): ν = 3319, 1722, 1895, 1605, 1592. Anal. Calc. for $C_{23}H_{21}ClN_4O_5$ (468.12): C, 58.91; H, 4.51; N, 11.95; Cl, 7.56. Found: C, 58.89; H, 4.48; N, 11.90; Cl, 7.47.

Entry 5 (4e). Solid, m.p. 196–198°C, ^{1}H NMR ($CDCl_3$): δ 1.22 (*t*, 3H, *J* = 7.0 Hz), 2.34 (*s*, 3H), 4.25 (*q*, 2H, *J* = 7.0 Hz), 4.81 (*s*, 1H), 6.78–8.92 (*m*, 8H, Ar—H), 9.24 (bs, 1H, NH), 10.67 (bs, 1H, NH). EMS: *m*/*z*: 465(M^+). IR (KBr): ν = 3470, 1725, 1682, 1602, 1573. Anal. Calc. for $C_{22}H_{19}N_5O_7$ (465.13): C, 56.77; H, 4.11; N, 15.05. Found: C, 56.75; H, 4.08; N, 15.04.

Entry 6 (4f). Solid, m.p. 209–210°C, ^{1}H NMR ($CDCl_3$): δ 1.21 (*t*, 3H, J = 7.0 Hz), 2.41 (*s*, 3H), 2.62(*s*, 3H), 4.00 (*q*, 2H, *J* = 7.0 Hz), 4.87 (s, 1H), 6.91 – 8.72 (*m*, 7H, Ar—H), 9.24 (bs, 1H, NH), 10.96 (bs, 1H, NH). EMS: *m*/*z*: 479(M^+). IR (KBr): ν = 3345, 1723, 1695, 1605, 1592. Anal. Calc. for $C_{23}H_{21}N_5O_7$ (479.14): C, 57.62; H, 4.41; N, 14.61. Found: C, 57.60; H, 4.38; N, 14.60.

Entry 7 (4g). Solid, m.p. 183–185°C, ^{1}H NMR ($CDCl_3$): δ 1.04 (*t*, 3H, *J* = 7.0 Hz), 2.41 (*s*, 3H), 2.65(*s*, 6H, $N(CH_3)_2$), 4.08 (*q*, 2H, *J* = 7.0 Hz), 4.83 (*s*,1H), 6.67–8.76 (*m*, 8H,

Ar—H), 9.18 (bs, 1H, NH), 10.86 (bs, 1H, NH). EMS: *m/z*: 463(M^+). IR (KBr): ν = 3295, 1714, 1677, 1611, 1575. Anal. Calc. for $C_{24}H_{25}N_5O_5$ (463.19): C, 62.19; H, 5.44; N, 15.10. Found: C, 62.17; H, 5.39; N, 15.09.

Entry 8 (4h). Solid, m.p. 188–190°C, ^{1}H NMR ($CDCl_3$): δ 1.19 (*t*, 3H, *J* = 7.0 Hz), 2.35 (*s*, 3H), 2.52(*s*, 3H), 2.67(*s*, 6H, $N(CH_3)_2$), 4.16 (*q*, 2H, *J* = 7.0 Hz), 4.78 (*s*,1H), 6.89–8.72 (*m*, 7H, Ar—H), 9.24 (bs, 1H, NH), 10.98 (bs, 1H, NH). EMS: *m/z*: 477(M^+). IR (KBr): ν = 3485, 1727, 1682, 1610, 1586. Anal. Calc. for $C_{25}H_{27}N_5O_5$ (477.2): C, 62.88; H, 5.70; N, 14.67. Found: C, 62.86; H, 5.23; N, 14.66.

Entry 9 (4i). Solid, m.p. 151–153°C, ^{1}H NMR ($CDCl_3$): δ 1.15 (*t*, 3H, *J* = 7.0 Hz), 2.36 (*s*, 3H), 4.20 (*q*, 2H, *J* = 7.0 Hz), 4.84 (*s*, 1H), 6.91–8.72 (*m*, 8H, Ar—H), 9.24 (bs, 1H, NH), 10.78 (bs, 1H, NH), 11.12 (bs, 1H, OH). EMS: *m/z*: 436(M^+). IR (KBr): ν = 3395, 1716, 1680, 1614, 1581. Anal. Calc. for $C_{22}H_{20}N_4O_6$ (436.14): C, 60.55; H, 4.62; N, 12.84. Found: C, 60.53; H, 4.58; N, 12.83.

Entry 10 (4j). Solid, m.p. 167–168°C, ^{1}H NMR ($CDCl_3$): δ 1.08 (*t*, 3H, *J* = 7.0 Hz), 2.36 (*s*, 3H), 2.61(*s*, 3H), 4.12 (*q*, 2H, *J* = 7.0 Hz), 4.89 (s, 1H), 6.84–8.67 (*m*, 7H, Ar—H), 9.14 (bs, 1H, NH), 10.29 (bs, 1H, NH), 11.20 (bs, 1H,OH). EMS: *m/z*: 450(M^+). IR (KBr): ν = 3410, 1712, 1692, 1607, 1575. Anal. Calc. for $C_{23}H_{22}N_4O_6$ (450.15): C, 61.33; H, 4.92; N, 12.44. Found: C, 61.31; H, 4.88; N, 12.40.

Entry 11 (4k). Solid, m.p. 217–219°C, ^{1}H NMR ($CDCl_3$): δ 1.18 (*t*, 3H, *J* = 7.0 Hz), 2.24 (*s*, 3H), 4.23 (*q*, 2H, *J* = 7.0 Hz), 4.76 (*s*, 1H), 7.12–8.53 (m, 7H, Ar—H), 9.20 (bs, 1H, NH), 10.76 (bs, 1H, NH). EMS: *m/z*: 410(M^+). IR (KBr): ν = 3317, 1719, 1675, 1610, 1594. Anal. Calc. for $C_{20}H_{18}N_4O_6$ (410.12): C, 58.53; H, 4.42; N, 13.65. Found: C, 58.51; H, 4.38; N, 13.60.

Entry 12 (4l). Solid, m.p. 213–214°C, ^{1}H NMR ($CDCl_3$): δ 1.19 (*t*, 3H, *J* = 7.0 Hz), 2.37 (*s*, 3H), 2.65(*s*, 3H), 4.16 (*q*, 2H, *J* = 7.0 Hz), 4.78 (*s*, 1H), 7.19–8.42 (m, 6H, Ar—H), 9.75 (bs, 1H, NH), 10.95 (bs, 1H, NH). EMS: *m/z*: 424 (M^+). IR (KBr): ν = 3347, 1716, 1689, 1612, 1589. Anal. Calc. for $C_{21}H_{20}N_4O_6$ (424.14): C, 59.43; H, 4.75; N, 13.20. Found: C, 59.41; H, 4.71; N, 13.18.

Entry 13 (4m). Solid, m.p.178–180°C, ^{1}H NMR ($CDCl_3$): δ 1.24 (*t*, 3H, *J* = 7.0 Hz), 2.32 (*s*, 3H), 4.18 (*q*, 2H, *J* = 7.0 Hz), 4.81 (*s*, 1H), 6.74–8.92 (*m*, 9H, Ar—H), 9.42 (bs, 1H, NH), 10.29 (bs, 1H, NH). EMS: *m/z*: 436 (M^+). IR (KBr): ν = 3489, 1717, 1689, 1602, 1591, 1242. Anal. Calc. for $C_{22}H_{20}N_4O_4S$ (436.12): C, 60.54; H, 4.62; N, 12.84. Found: C, 60.53; H, 4.58; N, 12.80.

Entry 14 (4n). Solid, m.p. 161–163°C, ^{1}H NMR ($CDCl_3$): δ 1.10 (*t*, 3H, *J* = 7.0 Hz), 2.22 (*s*, 3H), 2.46(*s*, 3H), 4.18 (*q*, 2H, *J* = 7.0 Hz), 4.92 (*s*, 1H), 6.84–8.86 (*m*, 8H, Ar—H), 9.82 (bs, 1H, NH), 10.46 (bs, 1H, NH). EMS: *m/z*: 450 (M^+). IR (KBr): ν = 3310, 1723, 1685, 1612, 1592, 1256. Anal. Calc. for $C_{23}H_{22}N_4O_4S$ (450.14): C, 61.32; H, 4.92; N, 12.44. Found: C, 61.31; H, 4.88; N, 12.40.

Entry 15 (4o). Solid, m.p. 199–200°C, ^{1}H NMR ($CDCl_3$): δ 1.09 (*t*, 3H, *J* = 7.0 Hz), 2.39 (*s*, 3H), 4.24 (*q*, 2H, *J* = 7.0 Hz), 4.86 (*s*, 1H), 6.89–8.87 (*m*, 8H, Ar—H), 9.24 (bs, 1H, NH), 10.74 (bs, 1H, NH). EMS: *m/z*: 470 (M^+). IR (KBr): ν = 3320, 1721, 1686, 1608, 1584, 1262. Anal. Calc. for $C_{22}H_{19}ClN_4O_4S$ (470.93): C, 56.11; H, 4.07; N, 11.90; Cl, 7.53. Found: C, 56.05; H, 4.03;; N, 11.89; Cl, 7.43.

Entry 16 (4p). Solid, m.p. 189–191°C, ^{1}H NMR ($CDCl_3$): δ 1.21 (*t*, 3H, *J* = 7.0 Hz), 2.34 (*s*, 3H),2.61(*s*, 3H), 4.26 (*q*, 2H, *J* = 7.0 Hz), 4.87 (*s*, 1H), 6.69–8.78 (*m*, 7H, Ar—H), 9.56 (bs, 1H, NH), 10.84 (bs, 1H, NH). EMS: *m/z*: 484 (M^+). IR (KBr): ν = 3359, 1716, 1888, 1618, 1589, 1259. Anal. Calc. for $C_{23}H_{21}ClN_4O_4S$ (484.1): C, 56.96; H, 4.36; N, 11.55; Cl, 7.31. Found: C, 56.90; H, 4.33; N, 11.50, Cl, 7.22.

Entry 17 (4q). Solid, m.p. 191–193°C, ^{1}H NMR ($CDCl_3$): δ 1.18 (*t*, 3H, *J* = 7.0 Hz), 2.31 (*s*, 3H), 4.28 (*q*, 2H, J = 7.0 Hz), 4.76 (*s*, 1H), 6.82–8.88 (*m*, 8H, Ar—H), 9.21 (bs, 1H, NH), 10.89 (bs, 1H, NH). EMS: *m/z*: 491 (M^+). IR (KBr): ν = 3478, 1720, 1679, 1598, 1559, 1242. Anal. Calc. for $C_{22}H_{19}N_5O_6S$(481.11): C, 54.88; H, 3.98; N, 14.55. Found: C, 54.87; H, 3.94; N, 14.54.

Entry 18 (4r). Solid, m.p. 207–208°C, ^{1}H NMR ($CDCl_3$): δ 1.16 (*t*, 3H, *J* = 7.0 Hz), 2.39 (*s*, 3H), 2.58 (*s*, 3H), 4.09 (*q*, 2H, *J* = 7.0 Hz), 4.69 (*s*, 1H), 6.87–8.79 (*m*, 7H, Ar—H), 9.32 (bs, 1H, NH), 10.76 (bs, 1H, NH). EMS: *m/z*: 495 (M^+). IR (KBr): ν = 3338, 1724, 1689, 1611, 1582, 1256. Anal. Calc. for $C_{23}H_{21}N_5O_6S$ (495.12): C, 55.75; H, 4.27; N, 14.13. Found: C, 55.74; H, 4.24; N, 14.10.

Entry 19 (4s). Solid, m.p. 182–183°C, ^{1}H NMR ($CDCl_3$): δ 1.14 (*t*, 3H, *J* = 7.0 Hz), 2.46 (*s*, 3H), 2.58(*s*, 6H, $N(CH_3)_2$), 4.16 (*q*, 2H, *J* = 7.0 Hz), 4.74 (*s*, 1H), 6.69–8.59 (m, 8H, Ar—H), 9.24 (bs, 1H, NH), 10.89 (bs, 1H, NH). EMS: *m/z*: 479 (M^+). IR (KBr): ν = 3291, 1718, 1659, 1602, 1561, 1269. Anal. Calc. for $C_{24}H_{25}N_5O_4S$ (479.16): C, 60.11; H, 5.25; N, 14.60. Found: C, 60.10; H, 5.21; N, 14.56.

Entry 20 (4t). Solid, m.p. 185–187°C, ^{1}H NMR ($CDCl_3$): δ 1.21 (*t*, 3H, *J* = 7.0 Hz), 2.24 (*s*, 3H), 2.56 (*s*, 3H), 2.71 (*s*, 6H, $N(CH_3)_2$), 4.12 (q, 2H, *J* = 7.0 Hz), 4.69 (*s*,1H), 6.79 – 8.77 (*m*, 7H, Ar—H), 9.31 (bs, 1H, NH), 11.04 (bs, 1H, NH). EMS: *m/z*: 493 (M^+). IR (KBr): ν = 3481, 1718, 1675, 1602, 1569, 1262. Anal. Calc. for $C_{25}H_{27}N_5O_4S$ (493.18): C, 60.83; H, 5.51; N, 14.19. Found: C, 60.82; H, 5.47; N, 14.15.

Entry 21 (4u). Solid, m.p. 165–165°C, ^{1}H NMR ($CDCl_3$): δ 1.12 (*t*, 3H, *J* = 7.0 Hz), 2.46 (*s*, 3H), 4.26 (*q*, 2H, J = 7.0 Hz), 4.79 (s, 1H), 6.86–8.82 (*m*, 8H, Ar—H), 9.36 (bs, 1H, NH), 10.89 (bs, 1H, NH), 11.14(bs, 1H, OH). EMS: *m/z*: 452 (M^+). IR (KBr): ν = 3386, 1712, 1669, 1609, 1579, 1248. Anal. Calc. for $C_{22}H_{20}N_4O_5S$ (452.12): C, 58.40; H, 4.46; N, 12.38. Found: C, 58.39; H, 4.42; N, 12.35.

Entry 22 (4v). Solid, m.p. 171–173°C, ^{1}H NMR ($CDCl_3$): δ 1.10 (*t*, 3H, *J* = 7.0 Hz), 2.31 (*s*, 3H), 2.49(*s*, 3H), 4.08 (*q*, 2H, *J* = 7.0 Hz), 4.74 (*s*, 1H), 6.69–8.66 (*m*, 7H, Ar—H), 9.19 (bs, 1H, NH), 10.21 (bs, 1H, NH), 11.18 (bs, 1H,OH). EMS: *m/z*: 466 (M^+). IR (KBr): ν = 3402, 1718, 1688, 1598, 1563, 1253. Anal. Calc. for $C_{23}H_{22}N_4O_5S$ (466.13): C, 59.22; H, 4.75; N, 12.01. Found: C, 59.21; H, 4.71; N, 12.00.

Entry 23 (4w). Solid, m.p. 212–214°C, ^{1}H NMR ($CDCl_3$): δ 1.14 (*t*, 3H, *J* = 7.0 Hz), 2.29 (*s*, 3H), 4.21 (*q*, 2H, *J* = 7.0 Hz), 4.58 (*s*, 1H), 7.16–8.59 (*m*, 7H, Ar-H), 9.28 (bs, 1H, NH), 10.81 (bs, 1H, NH). EMS: *m/z*: 426 (M^+). IR (KBr): ν = 3326, 1723, 1665, 1612, 1598, 1264. Anal. Calc. for $C_{20}H_{18}N_4O_5S$ (426.1): C, 56.33; H, 4.25; N, 13.14. Found: C, 56.32; H, 4.22; N, 13.10.

Entry 24 (4x). Solid, m.p. 206–207°C, ^{1}H NMR ($CDCl_3$): δ 1.23 (*t*, 3H, *J* = 7.0 Hz), 2.41 (*s*, 3H), 2.71 (*s*, 3H), 4.12 (*q*, 2H, *J* = 7.0 Hz), 4.72 (*s*, 1H), 7.12–8.56 (*m*, 6H, Ar—H), 9.89 (bs, 1H, NH), 10.89 (bs, 1H, NH). EMS: *m/z*: 440 (M^+). IR (KBr): ν = 3352, 1721, 1679, 1603, 1576, 1261. Anal. Calc.

for $C_{21}H_{20}N_4O_5S$ (440.12): C, 57.26; H, 4.58; N, 12.72. Found: C, 57.25; H, 4.54; N, 12.70.

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