Utility of β-(4-Chlorobenzoyl)acrylic Acid in Heterocyclic Synthesis

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β-(4-Chlorobenzoyl)acrylic acid (**1**) proved to be a convenient precursor for the synthesis of a variety of heterocyclic systems through the reaction with compounds containing active methylene groups under Michael reaction conditions. Also, the reactivity of Michael adduct towards nitrogen nucleophiles was investigated to afford diazepine, indazole, isoxazole and quinazoline derivatives. Some of the synthesized compounds were screened for their biological activity.

Keywords: Indazole; Isoxazole; Michael adduct; Diazepine and quinazoline derivatives.

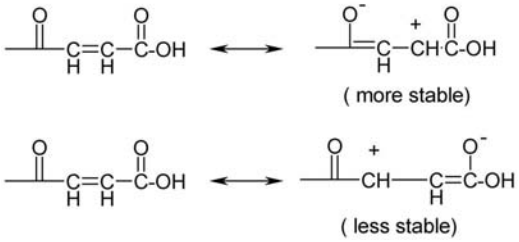
INTRODUCTION

α,β-Unsaturated γ-oxo acids play an essential role as key starting material in synthesis of some interesting and diverse heterocyclic compounds[1-5] with expected biological activity and have considerable chemical and pharmacological importance. Particularly, they are useful as antimicrobial,[6] antitumar,[7] cardiovascular[8] as well as agrochemical and veterinary products.[9] In view of the aforesaid versatile benefits and in conjunction of our interest in developing an efficient synthesis of polyfunctionally substituted heterocycles systems[10,11] we utilized the readily obtainable β-(4-chlorobenzoyl)acrylic acid as starting material. It is worthwhile to explore their potential utility for synthesis of polyfunctionally substituted heterocycles derivatives useful for optimization of biological activity.

RESULTS AND DISCUSSION

In the present work, the author focused on the investigation of Michael addition reaction of β-(4-chlorobenzoyl)-acrylic acid (**1**) with active methylene compounds, which was studied in order to ascertain the mode of addition of activated methylene compounds, since **1** could behave as an α,β-unsaturated acid or as an α,β-unsaturated ketone. Thus, it was found in the present work, the acid **1** underwent Michael addition with active methylene compounds (*viz.* ethylacetoacetate, acetylacetone, ethylcyanoacetate, camphor, cyclohexanone, ethyl phenylacetate, diethylmalonate and malononitrile) in the presence of (NaOH/EtOH) at room temperature to afford Michael adducts **2a-h** respectively.

It has been found that in these acids the polarization of the olefinic double bond by a ketone group outweighs that caused by the carboxylic group, the keto group giving a more stable carbonium ion than the carboxyl group,[12] that is, the α-carbon atom accepts the nucleophiles (donor in Michael addition) more readily than the β-carbon atom.



Recently, significant progress has been made in the development of antiviral chemotherapy due to pyrazole and diazepine derivatives.[13-16] Accordingly, the condensation of Michael adducts **2a** and **2b-h** with hydrazines (*viz.* hydrazine hydrate and phenyl hydrazine) in refluxing ethanol afforded 4-(4-chlorophenyl)-2-(3-methyl-5-oxo-1H/phenyl-4,5-dihydro-1H-pyrazol-4-yl)-4-oxobutyric acid (**3a,b**) and diazepine derivatives (**4a,b** to **10a, b**), respectively (Scheme I).

An even more convenient access to the synthesis of heterocyclic compounds of biological interest was established by fusion of β-(4-chlorobenzoyl)acrylic acid with acetyl acetone in the presence of sodium methoxide to give a mixture of 6-acetyl-3-(4-chlorophenyl)-5-oxo-cyclohex-3-ene carboxylic acid (**11**) and 3,3-diacetyl-2,4-bis[2-(4-chlorophenyl)-2-oxoethyl]pentanedioic acid (**12**).

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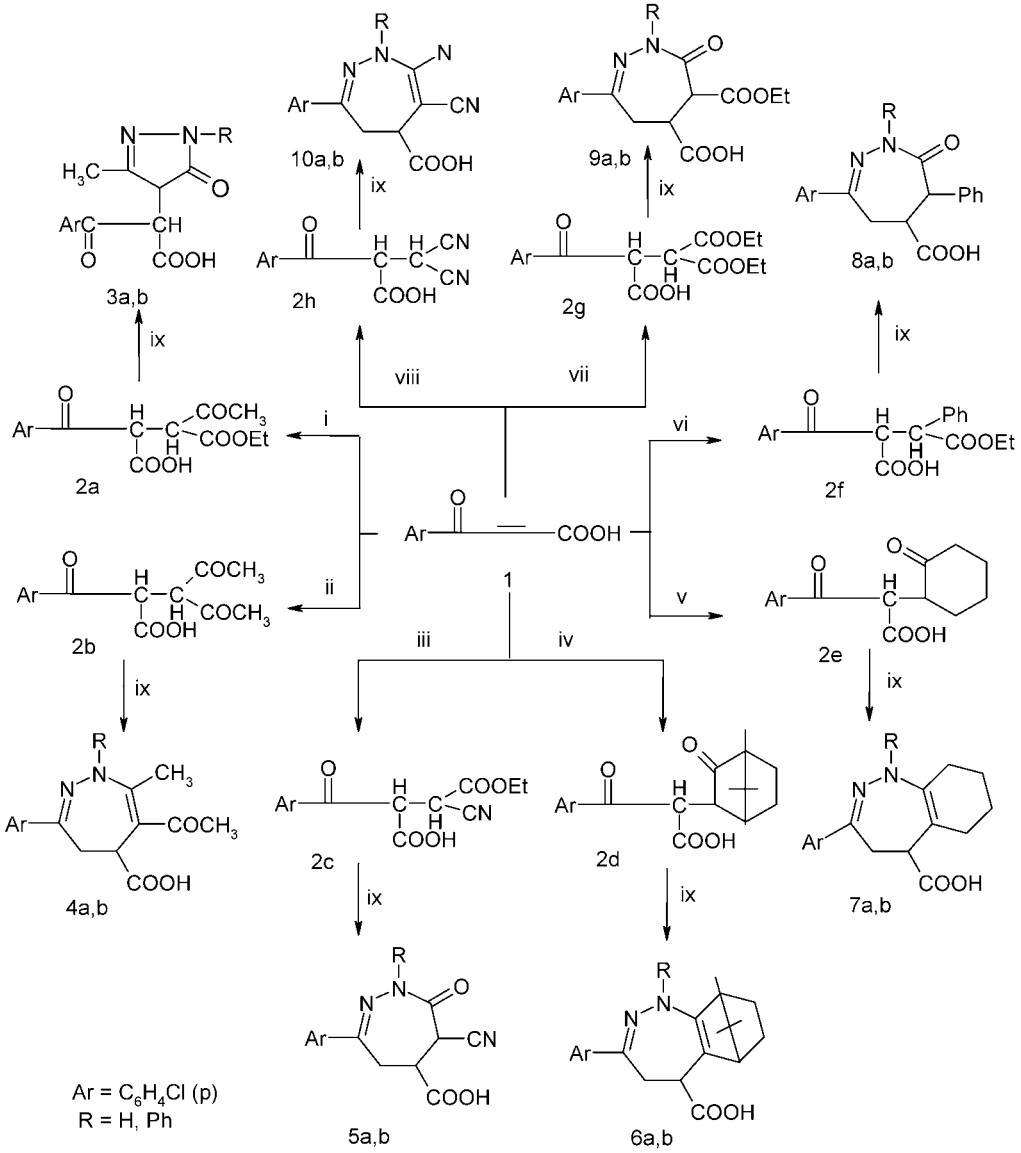
Scheme I

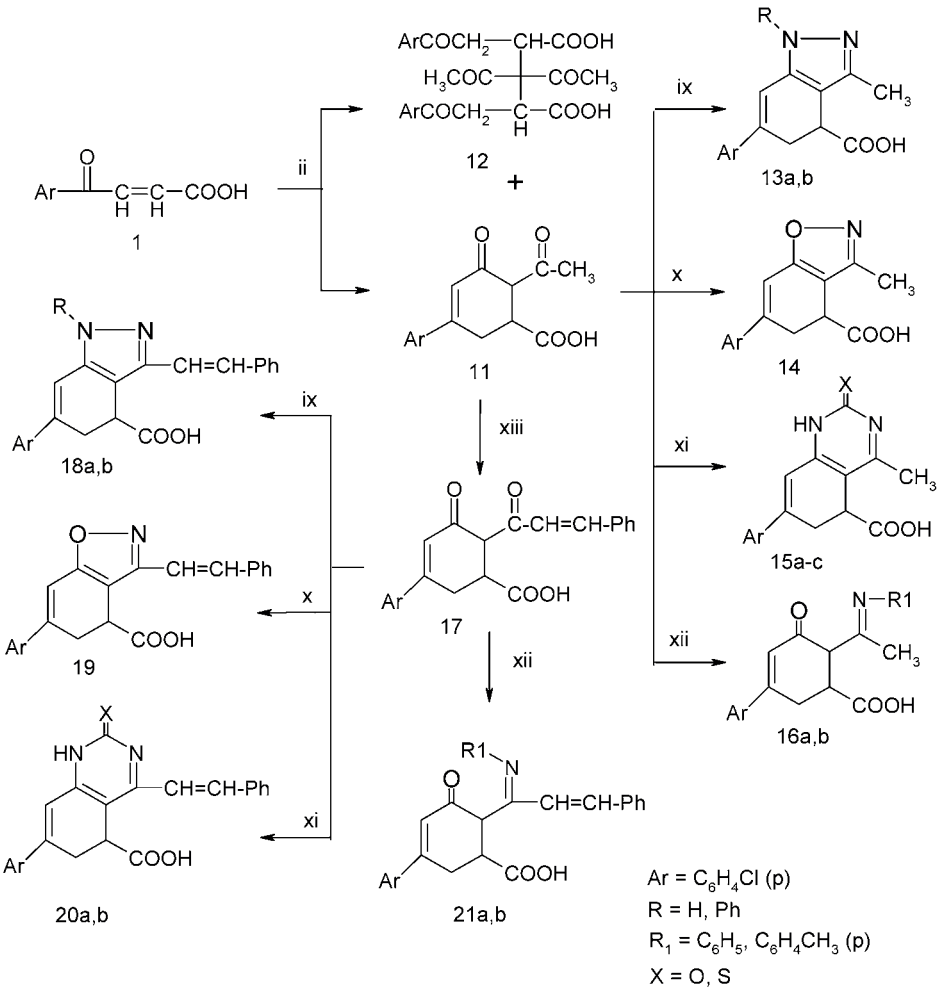


Reagents: i, CH_3COCH_2COOEt; ii, Ac_2CH_2; iii, $CNCH_2COOEt$; iv, camphor; v, cyclohexanone; vi, $PhCH_2COOEt$; vii, $CH_2(COOEt)_2$; viii, $CH_2(CN)_2$; ix, $RNHNH_2$

As an extension of this synthetic route, compound **11** was used as a target for construction of biologically active indazole,[17] benzisoxazole[18-20] and quinazoline derivatives[21-23] through the reaction with nitrogen nucleophiles. Thus, the reaction of **11** with hydrazines (*viz.* hydrazine hydrate and phenyl hydrazine) gave indazole derivatives **13a,b** but the condensation of **11** with hydroxylamine hydrochloride in boiling pyridine afforded 6-(4-chlorophenyl)-3-methyl-4,5-dihydrobenzo[d]isoxazole-4-carboxylic acid (**14**). Condensation of **11** with urea and/or thiourea afforded quinazoline derivatives **15a,b**. Also, the reaction of **11** with aromatic amines (*viz*. aniline and/or *p*-methylaniline) gave (**16a,b**).

Cinnamoylcyclohexanone **17** which contains a toxophoric system structure was synthesized from the condensation of **11** with benzaldehyde which reacts with hydrazine hydrate, phenyl hydrazine, hydroxylamine hydrochloride, urea and/or thiourea to afford new series of indazole, benzoisoxazole and quinazoline derivatives **18a,b,19,20a,b**, respectively, having a toxophoric system type structural hopping to increase the biological activities of these synthesized compounds (Scheme II).

Scheme II



Reagents: ii, Ac_2CH_2; ix, $RNHNH_2$; x, H_2NOH; xi, H_2NCXNH_2; xii, $R1NH_2$; xiii, PhCHO

BIOLOGICAL ACTIVITY

The antimicrobial activity of the synthesized compounds was determined *in vitro* using the hole plate and filter paper method.[24] All compounds were tested for activity against gram positive, gram negative bacteria and selected fungi. A quantitative screen was performed on all compounds and the results are listed in Table 1.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. IR spectra in KBr were recorded on a Shimadzu 470 spectrophotometer. ^{1}H NMR spectra in DMSO-d_6 were recorded on a Varian Gemini, 200 MHz (chemical shifts are expressed as δ, ppm) and the mass spectra were obtained on a Shimadzu GCMS QP 1000 Ex mass spectrometer (70 eV EI mode).

β-(4-Chlorobenzoyl)acrylic acid (1)[25]

Anhydrous aluminum chloride (130 mmol) was added portionwise to a stirred solution of maleic anhydride (85 mmol) in *p*-chlorobenzene (85 mmol) in an ice bath. The whole mixture was stirred at room temperature for a further 6 h, then left to stand overnight. The precipitated solid after addition of ice cold hydrochloric acid (25 mL) was filtered off, dried and the crude product was recrystallized from benzene to give **1**. (80% yield) yellow crystals, m.p. 128-130 °C. IR: 3100-3350 (broad) (OH), 1693 (C=O) and 1588 cm^{-1} (C=C); MS: *m/z* (%) M^++1 = 211 (33). Anal calcd for $C_{10}H_7O_3Cl$ (210.62): C, 57.03; H, 3.35%. Found: C, 57.09; H, 3,41%.

Table 1. Activity (A) and minimum inhibitory concentration (MIC) calculated as μg/mL for compounds (**2-20**)

Compd. No.	*Bacillus subtilis*		*Bacillus cereus*		*Escherichia coli*		*Aspergillus niger*	
	A	MIC	A	MIC	A	MIC	A	MIC
2a	+	500	+	250	+	125	-	-
2b	++	250	+	250	++	500	+	250
2c	+	125	++	250	+	250	+	500
2d	+	250	++	250	+	125	++	125
2e	+	250	+	125	+	125	-	-
2f	+	250	+	125	+	250	+	250
2g	+	500	+	250	+	125	-	-
3a	++	250	++	125	++	250	+	500
3b	+	125	+	250	+	125	-	-
4a	+	500	+	250	+	125	-	-
4b	++	250	+	250	++	500	+	250
5a	+	125	++	250	+	250	+	500
5b	+	250	++	250	+	125	++	125
6a	+	250	+	125	+	125	-	-
6b	+	250	+	125	+	250	+	250
7a	+	500	+	250	+	125	-	-
7b	++	250	++	125	++	250	+	500
8a	+	125	+	250	+	125	-	-
8b	+	500	+	250	+	125	-	-
9a	++	250	+	250	++	500	+	250
9b	+	125	++	250	+	250	+	500
10a	+	250	++	250	+	125	++	125
10b	+	250	+	125	+	125	-	-
11	+	250	+	125	+	250	+	250
12	+	500	+	250	+	125	-	-
13a	++	250	++	125	++	250	+	500
13b	++	250	+	250	++	500	+	250
14	++	250	+	250	++	500	+	250
15a	+	125	+	250	+	125	-	-
15b	+	500	+	250	+	125	-	-
16a	++	250	+	250	++	500	+	250
16b	+	125	++	250	+	250	+	500
17	+	250	++	250	+	125	++	125
18a	+	250	+	125	+	125	-	-
18b	+	250	+	125	+	250	+	250
19	+	500	+	250	+	125	-	-
20a	++	250	++	125	++	250	+	500
20b	++	250	+	250	++	500	+	250
21a	++	250	+	250	++	500	+	250
21b	++	250	+	250	++	500	+	250

A = Antimicrobial activity of tested compounds.
MIC = Minimum inhibitory concentration (units).
+ > 5 mm slightly active, ++ > 7 mm moderately active, +++ > 9 mm highly active.

General procedure of the reaction of β-(4-chlorobenzoyl)acrylic acid (1) with active methylene compounds: Formation of 2a-h

A mixture of **1** (2.25 g, 0.01 mol), the active methylene compound, namely ethyl acetoacetate, acetyl acetone, ethyl-cyanoacetate, camphor, cyclohexanone, ethyl phenyl acetate, diethylmalonate and malononitrile (0.02 mol) in ethanol (30 mL), was treated with sodium hydroxide (3g, 6 mL). The reaction mixture was heated at 40 °C for 24 h and then left overnight at room temperature (in the case of ethyl acetoacetate or

ethyl phenyl acetate, the reaction mixture was refluxed for 3 h). The reaction mixture was concentrated, diluted with water (70 mL) and extracted with ether (100 mL). The aqueous layer was acidified with ice-cold dil. HCl (100 g/20 mL), and extracted with ether (150 mL). Slow evaporation of dried ether gave a solid which crystallized from a proper solvent to give the colorless Michael adducts **2a-h**.

2-Acetyl-3-[2-(4-chlorophenyl)-2-oxoethyl]-succinic acid 1-ethyl ester (2a)

(70% yield) yellow crystals, m.p. 350-352 °C. IR: 3470-3300 (OH), 1732 (C=O of ester), 1680-1670 cm^{-1} (C=O of acid and ketone); ^1H NMR ($CDCl_3$) δ: 1.7 (t, 3H, $\underline{CH_3}CH_2$), 2.95 (q, 2H, $CH_2\underline{CH_3}$), 3.1 (t, 1H, CH), 3.4 (s, 3H, $COCH_3$), 4.21 (d, 2H, $\underline{CH_2}CH$), 7.01-8.13 (m, 4H, ArH), 10.21 (s, 1H, OH exchangeable). Anal calcd for $C_{16}H_{17}O_6Cl$ (340.76): C, 56.40; H, 5.03%. Found: C, 56.45; H, 5.09%.

3-Acetyl-2-[2-(4-chlorophenyl)-2-oxoethyl]-4-oxopentanoic acid (2b)

(65% yield) brown crystals, m.p. 280-282 °C. IR: 3490-3400 (OH), 1728 (C=O of ester) and 1681-1675 cm^{-1} (C=O of acid and ketone); MS: *m/z* (%) M^+ = 310 (24). Anal calcd for $C_{15}H_{15}O_5Cl$ (310.74): C, 57.98; H, 4.87%. Found: C, 57.74; H, 4.80%.

2-[2-(4-Chlorophenyl)-2-oxoethyl]-3-cyanosuccinic acid 4-ethyl ester (2c)

(60% yield) deep yellow crystals, m.p. 333-335 °C. IR: 3454-3212 (OH), 2241 (C=N), 1734 (C=O of ester) and 1690-1685 cm^{-1} (C=O of acid and ketone); MS: *m/z* (%) M^+-2 = 321 (27). Anal calcd for $C_{15}H_{14}NO_5Cl$ (323.74): C, 55.65; H, 4.36; N, 4.33%. Found: C, 55.68; H, 4.25%.

4-(4-Chlorophenyl)-4-oxo-2-(4,7,7-trimethyl-3-oxobicyclo-[2.2.1]hept-2-yl)butyric acid (2d)

(72% yield) pale yellow crystals, m.p. 100-102 °C. IR: 3430-3200 (OH), 1739 (C=O of ester) and 1685 cm^{-1} (C=O of acid); Anal calcd for $C_{20}H_{23}O_4Cl$ (362.86): C, 66.20; H, 6.39%. Found: C, 66.25; H, 6.43%.

4-(4-Chlorophenyl)-4-oxo-2-(2-oxo-cyclohexyl)butyric acid (2e)

(65% yield) pale yellow crystals, m.p. 200-202 °C. IR: 3460-3300 (OH), 1728 (C=O of ester) and 1690-1682 cm^{-1} (C=O of acid and ketone); MS: *m/z* (%) M^++1 = 309 (35). Anal calcd for $C_{16}H_{17}O_4Cl$ (308.76): C, 62.24; H, 5.55%. Found: C, 62.27; H, 5.59%.

2-[2-(4-Chlorophenyl)-2-oxoethyl]-3-phenylsuccinic acid 4-ethyl ester (2f)

(68% yield) yellow crystals, m.p. 265-267 °C. IR: 3400-3210 (OH), 1735 (C=O of ester) and 1700-1690 cm^{-1} (C=O of acid and ketone); Anal calcd for $C_{20}H_{19}O_5Cl$ (374.82): C, 64.09; H, 5.11%. Found: C, 64.00; H, 5.00%.

3-Carboxy-5-(4-chlorophenyl)-2-ethoxycarbonyl-5-oxo-pentanoic acid ethyl ester (2g)

(65% yield) white yellow crystals, m.p. 244-246 °C. IR: 3430-3310 (OH), 1740-1730 (C=O of esters) and 1685-1670 cm^{-1} (C=O of acid and ketone); Anal calcd for $C_{17}H_{19}O_7Cl$ (370.79): C, 55.07; H, 5.17%. Found: C, 55.11; H, 5.22%.

2-[2-(4-Chlorophenyl)-2-oxoethyl]-3,3-dicyanopropionic acid (2h)

(62% yield) deep yellow crystals, m.p. 273-275 °C. IR: 3420-3300 (OH), 2260-2250 (2 C=N), and 1690-1680 cm^{-1} (C=O of acid and ketone); Anal calcd for $C_{13}H_9N_3O_3Cl$ (276.68): C, 56.43; H, 3.28; N, 10.12%. Found: C, 56.48; H, 3.32; N, 10.16%.

General procedure for the reaction of 2a with hydrazines

A solution of **2a** (0.005 mol) in ethanol (30 mL) was treated with hydrazines, namely (hydrazine hydrate and phenyl hydrazine) (0.005 mol), and the solution refluxed for 4 h. The solid product formed after concentration and cooling was crystallized from an appropriate solvent to give **3a** and **3b**.

4-(4-Chlorophenyl)-2-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxobutyric acid (3a)

(60% yield) deep yellow crystals, m.p. 181-183 °C. IR: 3400-3200 (OH, NH), and 1690-1670 cm^{-1} (C=O of acid, ketone and amide); Anal calcd for $C_{14}H_{13}N_2O_4Cl$ (308.72): C, 54.47; H, 4.24; N, 9.07%. Found: C, 54.51; H, 4.29; N, 9.11%.

4-(4-Chlorophenyl)-2-(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-4-oxobutyric acid (3b)

(65% yield) yellow crystals, m.p. 168-170 °C. IR: 3460 (OH) and 1680-1677 cm^{-1} (C=O of acid, ketone and amide); MS: *m/z* (%) M^++2 = 386 (23). Anal calcd for $C_{20}H_{17}N_2O_4Cl$

(384.82): C, 62.42; H, 4.45; N, 7.28%. Found: C, 62.00; H, 4.50; N, 7.32%.

General procedure of formation of diazepine derivatives (4a,b-10a,b)

A solution of Michael adducts **2b-h** (0.005 mol) in *n*-butanol (30 mL) was treated with hydrazines, namely (hydrazine hydrate and phenyl hydrazine) (0.005 mol), and the solution refluxed for 4 h. The solid product formed after concentration and cooling was crystallized from an appropriate solvent to give (**4a,b-10a,b)**.

6-Acetyl-3-(4-chlorophenyl)-7-methyl-4,5-dihydro-1H-[1,2]diazepine-5-carboxylic acid (4a)

(62% yield) pale yellow crystals, m.p. 220-224 °C. IR: 3390-3200 (OH, NH) and 1695-1670 cm^{-1} (C=O of acid and ketone); ^1H NMR ($CDCl_3$) δ: 1.71 (s, 3H, CH_3), 1.5, 1.7 (d, 2H, CH_2 of the ring), 2.30 (s, 3H, $COCH_3$), 3.00 (t, 1H, CH-COOH), 7.00 (s, 1H, NH), 7.29-7.62 (m, 4H, ArH) and 11.00 (s, 1H, OH exchangeable). Anal calcd for $C_{15}H_{15}ClN_2O_3$ (306.74): C, 58.73; H, 4.93; N, 9.13%. Found: C, 58.51; H, 5.59; N, 9.11%.

6-Acetyl-3-(4-chlorophenyl)-7-methyl-1-phenyl-4,5-dihydro-1H-[1,2]diazepine-5-carboxylic acid (4b)

(66% yield) reddish yellow crystals, m.p. 192-194 °C. IR: 3395 (OH) and 1684-1663 cm^{-1} (C=O of acid and ketone); ^1H NMR ($CDCl_3$) δ: 1.70 (s, 3H, CH_3), 1.4, 1.7 (d, 2H, CH_2 of the ring), 2.30 (s, 3H, $COCH_3$), 3.01 (t, 1H, CH-COOH), 6.46-7.62 (m, 9H, ArH) and 11.00 (s, 1H, OH exchangeable). MS: *m/z* (%) M^++1 = 383 (32). Anal calcd for $C_{21}H_{19}ClN_2O_3$ (382.84): C, 65.88; H, 5.00; N, 7.23%. Found: C, 65.59; H, 5.54; N, 7.33%.

3-(4-Chlorophenyl)-6-cyano-7-oxo-4,5,6,7-tetrahydro-1H-[1,2]diazepine-5-carboxylic acid (5a)

(85% yield) white yellow crystals, m.p. 178-180 °C. IR: 3410-3320 (OH, NH), 2240 (C=N) and 1680-1665 cm^{-1} (C=O of acid, ketone and amide); Anal calcd for $C_{13}H_{10}N_3O_3Cl$ (291.70): C, 53.53; H, 3.46; N, 14.41%. Found: C, 53.57; H, 3,49; N, 14.45%.

3-(4-Chlorophenyl)-6-cyano-7-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-[1,2]diazepine-5-carboxylic acid (5b)

(60% yield) pale yellow crystals, m.p. 160-162 °C. IR: 3420 (OH), 2230 (C=N) and 1680-1665 cm^{-1} (C=O of acid, ketone and amide); ^1H NMR ($CDCl_3$) δ: 4.11 (d, 2H, CH_2), 3.31, 5.11 (d, 2H, 2 methine proton), 6.96-7.95 (m, 9H, ArH), 10.62 (s, 1H, OH exchangeable). Anal calcd for $C_{19}H_{14}N_3O_3Cl$ (367.79): C, 62.05; H, 3.84; N, 11.42%. Found: C, 62.09; H, 3.87; N, 11.45%.

3-(4-Chlorophenyl)-9,10,10-trimethyl-4,5,6,7,8,9-hexahydro-1H-6,9-methano-benzo[c][1,2]diazepine-5-carboxylic acid (6a)

(59% yield) yellow crystals, m.p. 240-242 °C. IR: 3420-3250 (OH, NH) and 1685 cm^{-1} (C=O of acid); Anal calcd for $C_{20}H_{23}N_2O_2Cl$ (358.87): C, 66.94; H, 6.46; N, 7.81%. Found: C, 66.97; H, 6.50; N, 7.84%.

3-(4-Chlorophenyl)-9,10,10-trimethyl-1-phenyl-4,5,6,7,8,9-hexahydro-1H-6,9-methanobenzo[c][1,2]diazepine-5-carboxylic acid (6b)

(68% yield) pale yellow crystals, m.p. 180-182 °C. IR: 3400 (OH) and 1683 cm^{-1} (C=O of acid); MS: *m/z* (%) M^+-2 = 332 (25). Anal calcd for $C_{26}H_{27}N_2O_2Cl$ (334.97): C, 71.80; H, 6.26; N, 6.44%. Found: C, 71.84; H, 6.30; N, 6.47%.

3-(4-Chlorophenyl)-4,5,6,7,8,9-hexahydro-1H-benzo[c][1,2]-diazepine-5-carboxylic acid (7a)

(63% yield) pale yellow crystals, m.p. 157-159 °C. IR: 3405-3230 (OH, NH) and 1690 cm^{-1} (C=O of acid); Anal calcd for $C_{16}H_{17}N_2O_2Cl$ (304.78): C, 63.05; H, 5.62; N, 9.19%. Found: C, 63.08; H, 5.65; N, 9.22%.

3-(4-Chlorophenyl)-1-phenyl-4,5,6,7,8,9-hexahydro-1H-benzo[c][1,2]diazepine-5-carboxylic acid (7b)

(60% yield) yellow crystals, m.p. 141-143 °C. IR: 3420 (OH) and 1682 cm^{-1} (C=O of acid); ^1H NMR (DMSO) δ: 2.21-3.81 (m, 8H, 4 CH_2), 3.31 (t, 1H, CH), 4.96 (d, 2H, CH_2), 7.02-8.13 (m, 9H, ArH), 10.26 (s, 1H, OH exchangeable). Anal calcd for $C_{22}H_{21}N_2O_2Cl$ (380.88): C, 69.38; H, 5.56; N, 7.35%. Found: C, 69.41; H, 5.59; N, 7.38%.

3-(4-Chlorophenyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydro-1H-[1,2]diazepine-5-carboxylic acid (8a)

(66% yield) pale yellow crystals, m.p. 230-232 °C. IR: 3390-3180 (OH, NH), and 1690-1675 cm^{-1} (C=O of acid and amide); Anal calcd for $C_{18}H_{15}N_2O_3Cl$ (342.78): C, 63.07; H, 4.41; N, 8.17%. Found: C, 63.11; H, 4.44; N, 8.21%.

3-(4-Chlorophenyl)-7-oxo-1,6-diphenyl-4,5,6,7-tetrahydro-1H-[1,2]diazepine-5-carboxylic acid (8b)

(72% yield) yellow crystals, m.p. 199-201 °C. IR: 3392

(OH), and 1692-1676 cm^{-1} (C=O of acid and amide); Anal calcd for $C_{24}H_{19}N_2O_3Cl$ (418.88): C, 68.82; H, 4.57; N, 6.69%. Found: C, 68.85; H, 4.60; N, 6.72%.

7-(4-Chlorophenyl)-3-oxo-3,4,5,6-tetrahydro-2H-[1,2]diazepine-4,5-dicarboxylic acid 4-ethyl ester (9a)

(64% yield) pale yellow crystals, m.p. 120-122 °C. IR: 3400-3210 (OH, NH), 1735 (C=O of ester) and 1690-1665 cm^{-1} (C=O of acid and amide); MS: *m/z* (%) M^++2 = 340 (33). Anal calcd for $C_{15}H_{15}N_2O_5Cl$ (338.75): C, 53.19; H, 4.46; N, 8.27%. Found: C, 53.22; H, 4.50; N, 8.30%.

7-(4-Chlorophenyl)-3-oxo-2-phenyl-3,4,5,6-tetrahydro-2H-[1,2]diazepine-4,5-dicarboxylic acid 4-ethyl ester (9b)

(60% yield) yellow crystals, m.p. 100-101 °C. IR: 3420 (OH), 1731 (C=O of ester) and 1684-1675 cm^{-1} (C=O of acid and amide); Anal calcd for $C_{21}H_{19}N_2O_5Cl$ (414.85): C, 60.80; H, 4.62; N, 6.75%. Found: C, 60.61; H, 4.40; N, 6.78%.

3-(4-Chlorophenyl)-6-cyano-7-oxo-4,5,6,7-tetrahydro-1H-[1,2]diazepine-5-carboxylic acid (10a)

(62% yield) pale yellow crystals, m.p. 162-164 °C. IR: 3410-3190 (OH, NH), 2235 (C=N) and 1690 cm^{-1} (C=O of acid); ^1H NMR ($CDCl_3$) δ: 4.16 (d, 2H, CH_2), 5.23 (t, 1H, CH), 6.21 (br s, 2H, NH_2), 6.98-8.23 (m, ArH and NH), 10.51 (s, 1H, OH exchangeable). Anal calcd for $C_{13}H_{10}N_3O_3Cl$ (291.70): C, 53.53; H, 3.46; N, 14.41%. Found: C, 53.56; H, 3.49; N, 14.44%.

3-(4-Chlorophenyl)-6-cyano-7-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-[1,2]diazepine-5-carboxylic acid (10b)

(58% yield) reddish yellow crystals, m.p. 149-151 °C. IR: 3450 (OH), 3195 (NH), 2235 (C≡N) and 1685 cm^{-1} (C=O of acid); Anal calcd for $C_{19}H_{14}N_3O_3Cl$ (367.79): C, 62.05; H, 3.84; N, 11.42%. Found: C, 62.08; H, 3.89; N, 11.46%.

General procedure of the reaction of β-(4-chlorobenzoyl)-acrylic acid (1) with acetyl acetone: Formation of 11 and 12

A mixture of **1** (2.25 g, 0.01 mol), acetyl acetone (0.01 mol) and sodium methoxide (0.01 mol) was heated at 120 °C for 3 h. The yellow oil obtained was crystallized from suitable solvent to give **11**. Acidification of aqueous layer by very cold dilute hydrochloric acid gave a semisolid product which was extracted by ether; evaporation of ether gave a colorless solid which upon repeated crystallization from light petrol gave **12**.

6-Acetyl-3-(4-chlorophenyl)-5-oxocyclohex-3-ene carboxylic acid (11)

(68% yield) brown crystals, m.p. 180-182 °C. IR: 3420-3250 (OH) and 1712-1700 cm^{-1} (C=O of ketone); ^1H NMR (DMSO) δ: 2.2 (s, 3H, CH_3), 4.26 (d, 2H, CH_2), 3.3, 5.1 (2 d, 2H, 2 mthine proton), 6.98-8.41 (m, 5H, ArH and olifinic protons), 10.51 (s, 1H, OH exchangeable). Anal calcd for $C_{25}H_{22}O_8Cl_2$ (521.36): C, 57.60; H, 4.25%. Found: C, 57.59; H, 4.37%.

3,3-Diacetyl-2,4-bis[2-(4-chlorophenyl)-2-oxoethyl]pentanedioic acid (12)

(55% yield) brown crystals, m.p. 320-322 °C. IR: 3400-3200 (OH) and 1695-1670 cm^{-1} (C=O of acids and ketones); MS: *m/z* (%) M^++1 = 291 (41). Anal calcd for $C_{15}H_{13}O_4Cl$ (292.72): C, 61.55; H, 4.48%. Found: C, 61.64; H, 4.47%.

General procedure of the reaction of 11 with hydrazines

A solution of **11** (0.01 mol) and hydrazine hydrate or phenyl hydrazine (0.015 mol) in alcohol (30 mL) was heated under reflux for 3 h. The yellow products obtained after concentration and cooling were crystallized from a suitable solvent to give the indazoles **13a** and **13b**.

6-(4-Chlorophenyl)-3-methyl-4,5-dihydro-1H-indazole-4-carboxylic acid (13a)

(63% yield) pale yellow crystals, m.p. 350-352 °C. IR: 3400-3200 (OH, NH) and 1690 cm^{-1} (C=O); Anal calcd for $C_{15}H_{13}N_2O_2Cl$ (288.74): C, 62.40; H, 4.54; N, 9.70%. Found: C, 62.41; H, 4.73; N, 9.73%.

6-(4-Chlorophenyl)-3-methyl-1-phenyl-4,5-dihydro-1H-indazole-4-carboxylic acid (13b)

(73% yield) red brown crystals, m.p. 277-279 °C. IR: 3410 (OH) and 1695 cm^{-1} (C=O); ^1H NMR (DMSO) δ: 2.1 (s, 3H, CH_3), 3.21 (t, 1H, CH), 4.22 (d, 2H, CH_2), 7.11-8.23 (m, 10H, ArH and olefinc protons), 10.51 (s, 1H, OH exchangeable). Anal calcd for $C_{21}H_{17}N_2O_2Cl$ (364.83): C, 69.14; H, 4.70; N, 7.68%. Found: C, 69.19; H, 4.73; N, 7.71%.

6-(4-Chlorophenyl)-3-methyl-4,5-dihydrobenzo[d]isoxazole-4-carboxylic acid 14

A solution of **11** (0.01 mol) and hydroxylamine hydrochloride (0.02 mol) in pyridine (20 mL) were heated under reflux for 4 h, then diluting with HCl gave the benzoisoxazole **14** which crystallized from ethyl alcohol. (66% yield) yellow crystals, m.p. 170-172 °C. IR: 3420-3350 (OH) and 1610

cm^{-1} (C=N); MS: *m/z* (%) M^+ = 289 (23). Anal calcd for $C_{15}H_{21}NO_3Cl$ (289.72): C, 62.19; H, 4.17; N, 4.83%. Found: C, 62.22; H, 4.20; N, 4.86%.

General procedure of the reaction of 11 with urea or thiourea

A cold solution of **11** (0.01 mol) and urea or thiourea (0.01 mol) in absolute ethanol (40 mL) was treated with conc. H_2SO_4 (2 mL). The mixture was acid for 24 h at room temperature. The reaction mixture was neutralized with $NaHCO_3$ solution. The products separated were crystallized from ethanol to give **15a** or **15b**.

7-(4-Chlorophenyl)-4-methyl-2-oxo-1,2,5,6-tetrahydroquinazoline-5-carboxylic acid (15a)

(59% yield) pale yellow crystals, m.p. 140-142 °C. IR: 3430-3210 (OH, NH), 1685-1670 (C=O of acid and amide); ^{1}H NMR (DMSO) δ: 1.93 (s, 3H, CH_3), 3.34 (t, 1H, CH), 3.97 (d, 2H, CH_2), 7.21-8.31 (m, 6H, ArH, olefinic and NH protons), 10.23 (s, 1H, OH exchangeable). Anal calcd for $C_{16}H_{13}N_2O_3Cl$ (316.75): C, 60.67; H, 4.14; N, 8.84%. Found: C, 60.76; H, 4.13; N, 8.88%.

7-(4-Chlorophenyl)-4-methyl-2-thioxo-1,2,5,6-tetrahydroquinazoline-5-carboxylic acid (15b)

(60% yield) reddish yellow crystals, m.p. 153-155 °C. IR: 3433-3215 (OH, NH), 1681-1670 (C=O of acid and amide) and 1265 cm^{-1} (C=S); Anal calcd for $C_{16}H_{13}N_2O_2ClS$ (332.81): C, 57.74; H, 3.94; N, 8.42; S, 9.63%. Found: C, 57.30; H, 3.97; N, 8.45; S, 9.67%.

General procedure of the reaction of 11 with amines

A solution of **11** (0.01 mol) and the amine, namely aniline and *p*-methyl aniline (0.015 mol) in alcohol (20 mL), were heated under reflux for 1 h. The products obtained after concentration and cooling were crystallized from a suitable solvent to give **16a** and **16b**.

3-(4-Chlorophenyl)-5-oxo-6-(1-phenylimino-ethyl)cyclohex-3-enecarboxylic acid (16a)

(65% yield) brown crystals, m.p. 190-192 °C. IR: 3390-3300 (OH, NH), 1705-1685 (C=O of acid and ketone) and 1610 cm^{-1} (C=N); Anal calcd for $C_{21}H_{18}NO_3Cl$ (367.84): C, 68.57; H, 4.93; N, 3.81%. Found: C, 68.60; H, 4.97; N, 3.85%.

3-(4-Chlorophenyl)-5-oxo-6-(1-*p*-tolylimino-ethyl)cyclohex-3-enecarboxylic acid (16b)

(72% yield) yellow crystals, m.p. 168-170 °C. IR: 3390 (OH), 1710-1685 (C=O of acid and ketone) and 1600 cm^{-1} (C=N); MS: *m/z* (%) M^+ = 381 (43). Anal calcd for $C_{22}H_{20}NO_3Cl$ (381.86): C, 69.20; H, 5.28; N, 3.67%. Found: C, 69.24; H, 5.32; N, 3.70%.

3-(4-Chlorophenyl)-5-oxo-6-(3-pheny-acryloyl)cyclohex-3-enecarboxylic acid (17)

A solution of **11** (0.01 mol), benzaldehyde (0.01 mol) and a few drops of piperidine in alcohol (30 mL) were heated under reflux for 4 h. The yellow products obtained after concentration and cooling were crystallized from ethanol to give **17**. (64% yield) pale yellow crystals, m.p. 210-212 °C. IR: 3400-3310 (OH), 1705-1690 (3 C=O of acid and ketone) and 1600 cm^{-1} (C=C); Anal calcd for $C_{22}H_{17}O_4Cl$ (380.83): C, 69.39; H, 4.50%. Found: C, 69.42; H, 4.54%.

General procedure of the reaction of 17 with hydrazines

A solution of **17** (0.01 mol) and hydrazine hydrate or phenyl hydrazine (0.015 mol) in alcohol (30 mL) were heated under reflux for 3 h. The yellow products obtained after concentration and cooling were crystallized from a suitable solvent to give the indazoles **18a** and **18b**.

6-(4-Chlorophenyl)-3-styryl-4,5-dihydro-1H-indazole-4-carboxylic acid (18a)

(57% yield) reddish yellow crystals, m.p. 187-189 °C. IR: 3435-3205 (OH, NH) and 1690 cm^{-1} (C=O); Anal calcd for $C_{22}H_{17}N_2O_2Cl$ (376.85): C, 70.12; H, 4.55; N, 7.43%. Found: C, 70.16; H, 4.58; N, 7.46%.

6-(4-Chlorophenyl)-1-phenyl-3-styryl-4,5-dihydro-1H-indazole-4-carboxylic acid (18b)

(57% yield) red brown crystals, m.p. 167-169 °C. IR: 3435 (OH) and 1699 cm^{-1} (C=O); MS: *m/z* (%) M^++1 = 453 (33). Anal calcd for $C_{28}H_{21}N_2O_2Cl$ (452.94): C, 74.25; H, 4.67; N, 6.18%. Found: C, 74.28; H, 4.70; N, 6.22%.

6-(4-Chlorophenyl)-3-styryl-4,5-dihydrobenzo[d]isoxazole-4-carboxylic acid (19)

A solution of **17** (0.01 mol) and hydroxylamine hydrochloride (0.02 mol) in pyridine (20 mL) were heated under reflux for 4 h, then diluted with HCl to give the benzoisoxazole **19** which crystallized from ethyl alcohol. (58% yield) yellow crystals, m.p. 89-91 °C. IR: 3410-3300 (OH) and 1685 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ: 3.21 (t, 1H, CH), 4.12 (d, 2H, CH_2), 6.98-8.11 (m, 12H, ArH and olefinic protons). Anal calcd for $C_{22}H_{16}NO_3Cl$ (377.83): C, 69.94; H, 4.27; N, 3.71%. Found: C, 69.97; H, 4.30; N, 3.75%

General procedure of the reaction of 17 with urea and thiourea

A cold solution of **17** (0.01 mol) and urea or thiourea (0.01 mol) in absolute ethanol (40 mL) was treated with conc. H_2SO_4 (2 mL). The mixture was left for 24 h at room temperature. The reaction mixture was neutralized with $NaHCO_3$ solution. The products separated were crystallized from ethanol to give **20a** and **20b**.

7-(4-Chlorophenyl)-2-oxo-4-styryl-1,2,5,6-tetrahydroquinazoline-5-carboxylic acid (20a)

(70% yield) yellow crystals, m.p. 170-172 °C. IR: 3410-3200 (OH), 1685-1675 (C=O of acid and amide) and 1590 cm^{-1} (C=C); Anal calcd for $C_{23}H_{17}N_2O_3Cl$ (404.86): C, 68.24; H, 4.23; N, 6.92%. Found: C, 68.28; H, 4.26; N, 6.95%.

7-(4-Chlorophenyl)-4-styryl-2-thioxo-1,2,5,6-tetrahydroquinazoline-5-carboxylic acid (20b)

(65% yield) pale yellow crystals, m.p. 166-168 °C. IR: 3420-3200 (OH), 1680-1675 (C=O of acid and ketone), 1591 (C=C) and 1255 cm^{-1} (C=S); ^1H NMR ($CDCl_3$) δ: 4.11 (d, 2H, CH_2), 4.39 (t, 1H, CH), 7.12-8.35 (m, 13H, ArH, olefinic and NH protons), 10.37 (s, 1H, OH exchangeable). Anal calcd for $C_{23}H_{17}N_2O_2ClS$ (420.92): C, 65.63; H, 4.07; N, 6.66; S, 7.62%. Found: C, 65.20; H, 4.11; N, 6.69; S, 7.65%.

General procedure of the reaction of 17 with amines

A solution of **17** (0.01 mol) and the amine, namely aniline and *p*-methyl aniline (0.015 mol) in alcohol (20 mL), were heated under reflux for 1 h. The products obtained after concentration and cooling were crystallized from a suitable solvent to give **21a** and **21b**.

3-(4-Chlorophenyl)-5-oxo-4-styryl-6-(1-phenyliminoethyl)-cyclohex-3-enecarboxylic acid (21a)

(60% yield) brown crystals, m.p. 179-181 °C. IR: 3390-3300 (OH, NH), 1705-1685 (C=O of acid and ketones) and 1610 cm^{-1} (C=N); MS: *m/z* (%) M^++1 = 456 (31). Anal calcd for $C_{28}H_{22}NO_3Cl$ (455.95): C, 73.76; H, 4.86; N, 3.07%. Found: C, 73.79; H, 4.90; N, 3.11%.

3-(4-Chlorophenyl)-5-oxo-4-styryl-6-(1-*p*-tolyliminoethyl)-cyclohex-3-enecarboxylic acid (21b)

(58% yield) pale yellow crystals, m.p. 162-164 °C. IR: 3340 (OH), 1705-1685 (C=O of acid and ketones) and 1610 cm^{-1} (C=N); Anal calcd for $C_{29}H_{24}NO_3Cl$ (469.97): C, 74.12; H, 5.15; N, 2.98%. Found: C, 74.15; H, 5.18; N, 3.01%.

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REFERENCES

1. Juranic, Z.; Stevovic, L. J.; Drakulic, B.; Stanojkovic, T.; Radulovic, S.; Juranic, I. *J. Serb. Chem. Soc*. **1999**, *64*, 505-512.
2. Wasfy, A. A.; Amine, M. S.; Arief, M. M. H.; Donia, S. G.; Aly, A. A. *Phosphorus, Sulfur and Silicon*. **2002**, *177*, 1359-1365.
3. Kalinin, A. A.; Mamedov, V. A. *J. Chemistry of Heterocyclic Compounds* **2004**, *40*, 129-131.
4. Hassan, H. M. *J. Serb. Chem. Soc*. **1998**, *63*, 117-123.
5. Soliman, A. Y.; Attia, I. A. *J. Serb. Chem. Soc*. **1998**, *63*, 909-913.
6. Koehler, T.; Friedrich, G.; Nuhn, P. *Agents Actions* **1991**, *32*, 70-72.
7. Koehler, T.; Heinisch, M.; Kirchner, M.; Peinhardt, G.; Hirsch-elmann, R.; Nuhn, P. *Biochem. Pharmacol*. **1992**, *44*, 805-813.
8. Bowden, K.; Dal Pozzo, A.; Duah, C. K. *J. Chem. Res.*, *Synop*. **1990**, *12*, 2801-2830.
9. Juranic, Z.; Stevovic, L. J.; Drakulic, B.; Stanojkovic, T.; Radulovic, S.; Juranic, I. *J. Serb. Chem. Soc*. **1999**, *64*, 505-512.
10. Eissa, A. M. F. *J. Heterocyclic Communications* **2003**, *9*, 181-188.
11. Amine, M. S.; Eissa, A. M. F.; Shaaban, A. F.; El-Sawy, A.; El-Sayed, R. *Indian J. Heterocycic. Chem.* **1998**, *7*, 289.
12. El-Hashash, M. A.; Mohamed, M. M.; Islam, I. E.; Abo-Baker, O. A. *Ind. J. Chem*. **1982**, *21B*, 735-739.
13. Sayed, G. H.; Ismail, A. A.; El-Mobayed, M.; Mohamed, S. M. *Commun. Fac. Sci. Univ. Ank. Series B* **1990**, *36*, 53-60.
14. Kidwai1, Ruby1 M.; Venkataramanan1, R.; Facile, A, *J. Chemistry of Heterocyclic Compounds* **2004**, *40*, 631-634.
15. Kosychova, L.; Stumbreviciute, Z.; Pleckaitiene, L.; Janciene, R.; Puodziunaite. B. D. *J. Chemistry of Heterocyclic Compounds* **2004**, *40*, 811-815
16. Tonkikh, N. N.; Strakovs, A.; Rizhanova, K. V.; Petrova, M. V. *J. Chemistry of Heterocyclic Compounds* **2004**, *40*, 949-955.
17. Khoshtariya, T. E.; Bochoidze, L. T.; Batsikadze, K. T. *J.*

Chemistry of Heterocyclic Compounds **2004**, *40*, 528-529.
18. Vovk, M. V.; Bol'but, A. V.; Lebed, P. S.; Boiko, V. I. *J. Chemistry of Heterocyclic Compounds* **2004**, *40*, 101-105.
19. Eissa, A. M. F.; El-Dougdoug, W. I. A.; El-Shenawy, A. I. *Egypt. J. Chem*. **2003**, *2*, 371-380.
20. Marzouk, M. I.; El-Hasash, M.; Eissa, A. M. F. *International. J. Chem*. **2002**, *12*,157-163.
21. Eissa, A. M. F. *Chemistry: An Indian Journal* **2003**, *1*, 17-21.
22. Wasfy, A. A. F.; Nassar, S. A.; Eissa, A. M. F. *Indian J. Chem*. **1996**, *35B*, 1218.
23. Amin, M. S.; Eissa, A. M. F.; Shaaban, A. F.; El-Sawy, A. A.; El-Sayed, R. *Ind. J. Chem.* **1998**, *37B*, 1153-1156.
24. Leifert, C.; Chidbouree, S.; Hampson, S.; Workman, S.; Sigee, D.; Epton, H. A. S.; Harbour, A. *J. Appl. Bact*. **1995**, *78*, 97.
25. Youssef, A. S. A.; Madkour, H. M. F.; Marzouk, M. I.; El-Soil, A. M. A.; El-Hashash, M. A. *Afinidad* **2003**, *61*, 304-316.