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SYNTHESIS OF SOME FUNCTIONALLY SUBSTITUTED DERIVATIVES ON THE BASE OF COMPOUNDS WITH ACTIVATED DOUBLE BOND

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Abstract. The Michael addition of benzoylacetone and ethyl-4-chloroacetoacetate to 2-(thiophene-2-carbonyl)-3-(p-tolyl)acrylonitrile was carried out. Corresponding 5-benzoyl-2-hydroxy-4-oxo-2-(thiophen-2-yl)-6-(p-tolyl)cyclohexane-1-carbonitrile and 3-chloro-5-cyano-4-hydroxy-2-oxo-4-(thiophen-2-yl)-6-(p-tolyl)cyclohexane-1-carboxylate were formed by these reactions. By the interaction of synthesized 5-benzoyl-2-hydroxy-4-oxo-2-(thiophen-2-yl)-6-(p-tolyl)cyclohexane-1-carbonitrile with hydrazine hydrate the bicyclic compound 6-hydroxy-3-phenyl-6-(thiophen-2-yl)-4-(p-tolyl)-3a,4,5,6-tetrahydro-1H-indazole-5-carbonitrile was formed. By the Michael addition of ethyl 4-chloroacetoacetate to 2-cyano-3-(4-fluorophenyl)acrylamide and 2-cyano-3-(thiophen-2-yl)acrylamide corresponding substituted pyridone derivatives were synthesized. Structures of all synthesized compounds confirmed by NMR spectroscopy.

Keywords: *Carbonylacrylonitriles, cyclohexanone, 1H-indazole, hidrazin hidrat, pyridone, NMR.*

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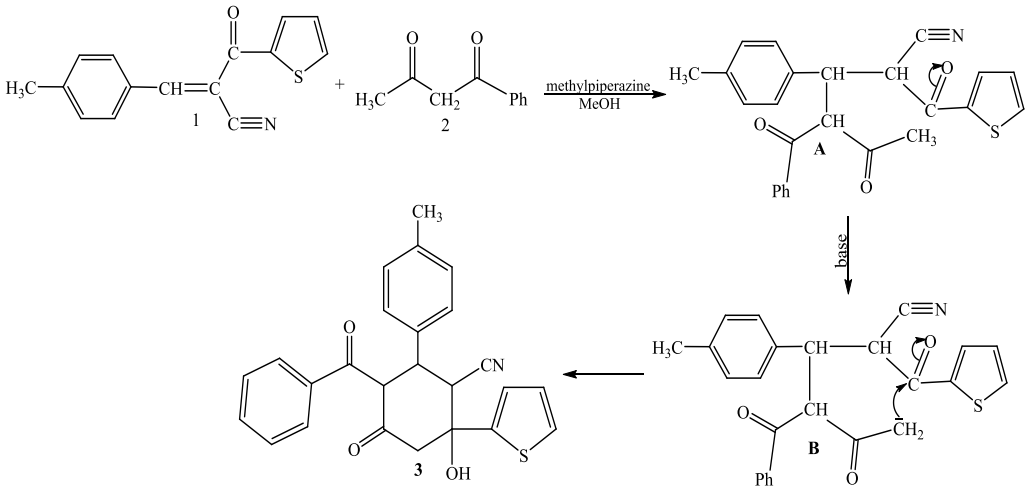
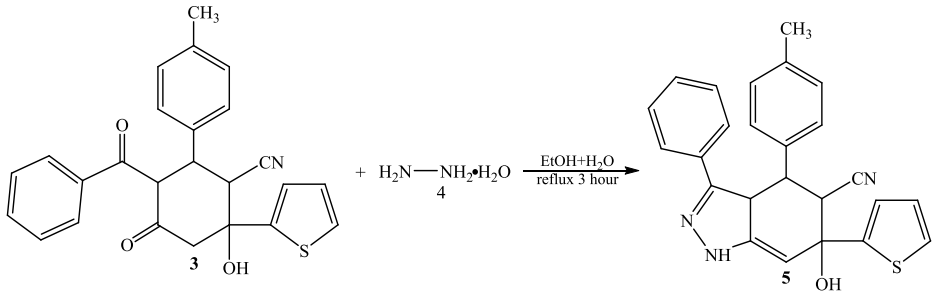
1. Introduction

There are informations about Michael addition of nucleophilic agents (methylene active compounds, enamines, diamines and etc) to compounds containing activated double bond in various conditions and cyclocondensation that formes new C−C, C−N, C−S bonds in synthesis of functionally substituted derivatives that formed by functionally substituted derivatives (Adib *et al.*, 2018; Naghiyev, 2019a, 2019b; Naghiyev *et al.*, 2020; Tahmassebi *et al.*, 2011; Kiruthika *et al.*, 2011; Tisseh *et al.*, 2012; Feng *et al.*, 2013; Pal *et al.*, 2015; Qiu *et al.*, 2010; Lakshmi *et al.*, 2012; Bardasov *et al.*, 2019; Quiroga *et al.*, 2001; Jadhav *et al.*, 2019; Li *et al.*, 2013; Mukhopadhyay *et al.*, 2011). Obtained in these reactions substituted pyridone, pyridine, pyrazole compound an potential biologically active compounds. So, there an papers (Nguyen *et al.*, 2019; Kanagarajan *et al.*, 2011; Gopalakrishnan *et al.*, 2009) about investigation of antimicrobic activites of cyclohexanones and 1H-indazole.

In presented work, we carried out Michael addition of benzoylacetone to 2-(thiophene-2-carbonyl)-3-(p-tolyl)acrylonitrile at room temperature, methanol media and in the presence of 1-methylpiperazine dropwise. 5-benzoyl-2-hydroxy-4-oxo-2-(thiophen-2-yl)-6-(p-tolyl)cyclohexane-1-carbonitrile (**3**) was formed in reaction. According to the proposal mechanism at first the corresponding Michael-adduct (intermediate **A**) was formed. Then by the action of base, intermediate **A** transforms to intermediate **B**. The reaction product (**3**) was obtained as a result of attack of carbanion CH_2 (nukleophilic agent) to carbon of carbonyl group.



By the interaction of 5-benzoyl-2-hydroxy-4-oxo-2-(thiophen-2-yl)-6-(p-tolyl)cyclohexane-1-carbonitrile (**3**) with hydrazine by reflux in ethanol-water media 6-hydroxy-3-phenyl-6-(thiophen-2-yl)-4-(p-tolyl)-3a,4,5,6-tetrahydro-1H-indazole-5-carbonitrile (**5**) was obtained. By our mind, nitrogen of hydrazine containing electron pair attacks as nucleophile to the carbon of carbonyl group and water eliminates so intermediate (corresponding hydrazine derivative) forms. The intermediate goes to enol-form and by elimination of other NH_2-group and water from enol gives reaction product (**5**).



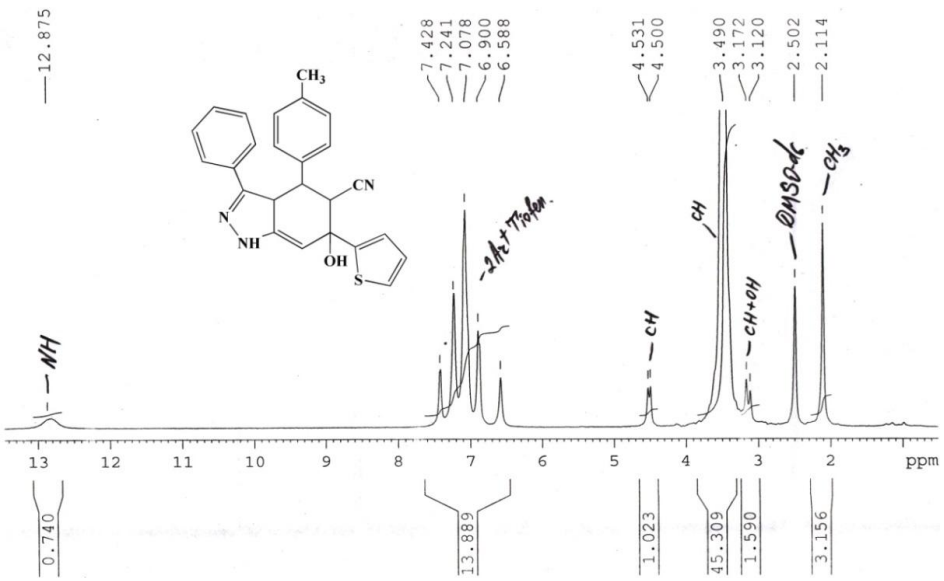
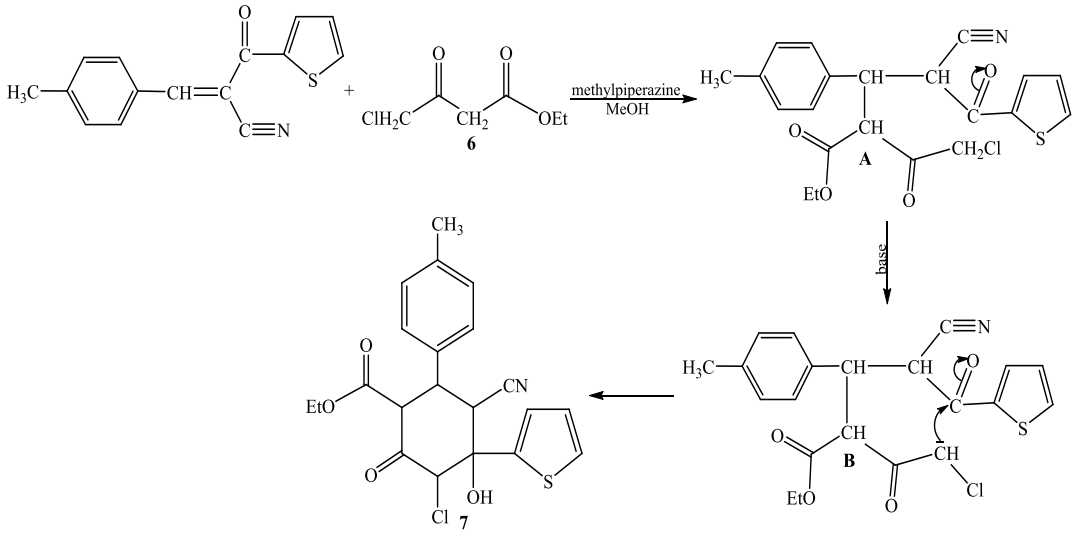
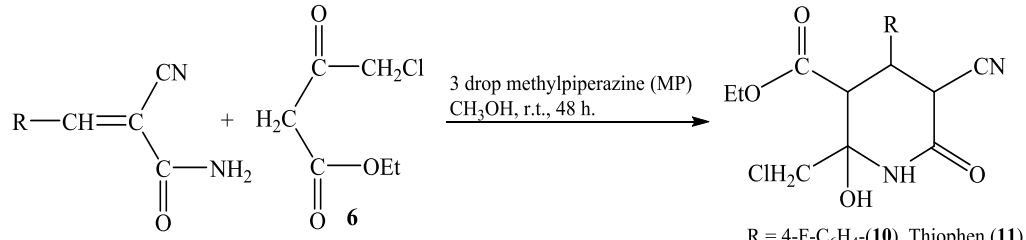


Figure 1. [1]H NMR spectrum of 6-hydroxy-3-phenyl-6-(thiophen-2-yl)-4-(p-tolyl)-3a, 4,5,6-tetrahydro-1H-indazole-5-carbonitrile (**5**)

The Michael addition of ethyl 4-chloroacetoacetate to 2-(thiophene-2-carbonyl)-3-(p-tolyl)acrylonitrile at the same conditions gives 3-chloro-5-cyano-4-hydroxy-2-oxo-4-(thiophen-2-yl)-6-(p-tolyl)cyclohexane-1-carboxylate. The possible mechanism of formation of (**7**) is the similar with (**3**).



We get corresponding substituted pyridone derivatives in satisfied yields by carring out of Michael addition of ethyl 4-chloroacetoacetate with 2-cyano-3-(4-fluoro-phenyl)acrylamide and 2-cyano-3-(thiophen-2-yl)acrylamide at the conditions shown above.



R = 4-F-C_6H_4-(**8**), Thiophen (**9**)

R = 4-F-C_6H_4-(**10**), Thiophen (**11**)

2. Experimental part. General remarks

All commercially available chemicals were obtained from Merck and Fluka (Sigma Aldrich) companies and used without further purification. Melting points were measured on an Stuart SMP30 apparatus without correction. ^{1}H, ^{13}C NMR spectra were recorded on Bruker Avance 300-MHz spectrometer at 300 and 75 MHz, respectively. Thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel (60 F254) was used to monitor the progress of reactions.

Experimental procedures:

5-Benzoyl-2-hydroxy-4-oxo-2-(thiophen-2-yl)-6-(p-tolyl)cyclohexane-1-carbonitrile (3): 1.29 g (5.1 mmol) 2-(thiophene-2-carbonyl)-3-(p-tolyl)acrylonitrile and 0.84 g (5.2 mmol) benzoylacetone stirrered in 35 ml of methyl alcohol. After adding of 3-4 drops of 1-methylpiperazine to reaction mixture and stirrered for 5-7 minutes. Then reaction mixture hold out at room temperature for 48 h. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 3:1). Crystals were precipitated after

evaporation of solvent, filtered, recrystallized from ethanol-water mixture and obtained in pure form (yield 1.80 g, 84.90%). $T_{mp.}$ = 295°C.

^{1}H NMR (300 MHz, DMSO-d_6): 2.18 (s, 3H, CH_3); 2.74 (d, 1H, CH, $^{3}J_{H-H}$ = 14.1); 3.43 (s, 1H, OH); 3.73 (t, 1H, CH, $^{3}J_{H-H}$ = 14.1); 4.07 (s, 2H, CH_2); 5.58 (d, 1H, CH, $^{3}J_{H-H}$ = 10.5); 7.07-7.80 (m, 12H, 9Ar−H+3$CH_{thienyl}$).

^{13}C NMR (75 MHz, DMSO-d_6): 21.02 ($\underline{CH_3}$−Ar), 44.55 ($\underline{CH}$−Ar), 48.34 ($\underline{CH}$−CN), 54.61 (CH_2), 61.14 ($\underline{CH}$−C=O), 75.48 (O−$\underline{C_{tert}}$), 118.66 (CN), 124.34 (CH_{arom}), 125.89 (CH_{arom}), 127.68 (CH_{arom}), 128.35 (2CH_{arom}), 128.46 (2CH_{arom}), 129.27 (2CH_{arom}), 129.64 (2$CH_{thienyl}$), 134.06 ($CH_{thienyl}$), 136.87 ($C_{ar.}$), 137.19 ($C_{ar.}$), 137.33 ($C_{ar.}$), 150.28 ($C_{thienyl}$), 196.42 ($\underline{C}$=O), 204.52 ($\underline{C}$=O).

6-Hydroxy-3-phenyl-6-(thiophen-2-yl)-4-(p-tolyl)-3a,4,5,6-tetrahydro-1H-indazole-5-carbonitrile (5): 2.12 g (0.0051 mol) 5-Benzoyl-2-hydroxy-4-oxo-2-(thiophen-2-yl)-6-(p-tolyl)cyclohexane-1-carbonitrile (**3**) 40 ml of ethanol in flask provided with freezer, thermometr and stirrer. Then excess of hydrazine hydrate added to reaction mixture and refluxed for 6 hours. Formed reaction mixture replaced to the glass. After evaporation of solvent, crystalls were precipitate. Crystalls were filtered, separated, recrystallized from ethanol (95%) - water mixture and dried. (yield 1.93 g, 91.90%). $T_{mp.}$ = 354°C.

^{1}H NMR (300 MHz, DMSO-d_6): 2.11 (s, 3H, CH_3); 3.15 (d, 2H, $\underline{CH}$ + $\underline{OH}$); 3.49 (t, 1H, $\underline{CH}$−Ar); 4.51 (d, 1H, $\underline{CH}$−CN, $^{3}J_{H-H}$ = 9.3); 6.59-7.43 (m, 12H, 9Ar−H + 3$CH_{thienyl}$); 12.87 (s, 1H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): 21.02 (CH_3), 40.68 ($\underline{CH}$), 41.70 ($\underline{CH}$−Ar), 50.59 ($\underline{CH}$−CN), 73.49 (O−$\underline{C_{tert}}$), 119.92 (CN), 123.86 ($\underline{CH}$=), 125.15 ($CH_{thienyl}$), 127.64 (4CH_{arom}), 127.76 ($CH_{thienyl}$),128.00 ($CH_{thienyl}$), 128.01 (3CH_{arom}), 128.79 (CH_{arom}),129.24 (CH_{arom}), 136.08 (2$C_{ar.}$), 138.45 ($C_{ar.}$ + $C_{thienyl}$), 152.29 (=$\underline{C_{tert}}$−NH), 152.35 (=$\underline{C_{tert}}$−NH).

Ethyl3-chloro-5-cyano-4-hydroxy-2-oxo-4-(thiophen-2-yl)-6-(p-tolyl)cyclohexane-1-carboxylate (7): 1.29 g (5.1 mmol) 2-(thiophene-2-carbonyl)-3-(p-tolyl)acrylonitrile and 0.86 g (5.2 mmol) ethyl 4-chloroacetoacetate stirrered in 35 ml of methyl alcohol. After adding of 3-4 drops of 1-methylpiperazine to reaction mixture and stirrered for 5-7 minutes. Then reaction mixture hold out at room temperature for 48 h. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 3:1). Crystals were precipitated after evaporation of solvent, filtered, recrystallized from ethanol-water mixture and obtained in pure form (yield 1.72 g, 80.75%). $T_{mp.}$ = 345°C.

^{1}H NMR (300 MHz, DMSO-d_6): 0.99 (t, 3H, CH_3, $^{3}J_{H-H}$=7.05); 2.28 (s, 3H, CH_3); 3.31 (s, 1H, OH); 3.79 (t, 1H, $\underline{CH}$−Ar, $^{3}J_{H-H}$ = 12.6); 3.94 (k, 2H, CH_2, $^{3}J_{H-H}$ = 6.9); 4.36 (t, 2H, $\underline{CH}$−CN + $\underline{CH}$−CO); 5.74 (s, 1H, $\underline{CH}$−Cl); 7.05-7.54 (m, 7H, 4Ar−H + 3$CH_{thienyl}$).

^{13}C NMR (75 MHz, DMSO-d_6): 14.26 (CH_3), 21.15 (CH_3), 44.10 (CH), 48.57 (CH), 61.02 (CH), 61.23 ($\underline{CH_2}$O), 72.84 ($\underline{CH}$−Cl), 79.68 (O−$\underline{C_{tert}}$), 117.77 (CN), 125.67 ($CH_{thienyl}$), 126.72 ($CH_{thienyl}$), 127.50 ($CH_{thienyl}$), 128.43 (2CH_{arom}), 129.84 (2CH_{arom}), 135.34 ($C_{ar.}$), 137.90 ($C_{ar.}$), 146.90 ($C_{thienyl}$), 167.09 ($\underline{C}$OO), 194.32 ($\underline{C}$=O).

Ethyl2-(chloromethyl)-5-cyano-4-(4-fluorophenyl)-2-hydroxy-6-oxopiperidine-3-carboxylate (10): 0.97 g (5.1 mmol) 2-Cyano-3-(4-fluorophenyl)acrylamide and 0.86 g (5.2 mmol) ethyl 4-chloroacetoacetate stirrered in 35 ml of methyl alcohol. After adding of 3 drops of 1-methylpiperazine to reaction

mixture and stirrered for 10 minutes. Then reaction mixture hold out at room temperature for 48 h. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 3:1). Crystals were precipitated after evaporation of solvent, filtered, recrystallized from ethanol-water mixture and obtained in pure form (yield 1.39 g, 76.79%). $T_{mp.}$ = 193°C.

^{1}H NMR (300 MHz, DMSO-d_6): 0.84 (t, 3H, CH_3, $^{3}J_{H-H}$ = 6.9); 3.61 (d, 1H, CH); 3.69 (s, 3H, $\underline{CH_2}Cl$); 3.79 (k, 2H, CH_2O); 3.88 (t, 1H, CH−Ar); 4.49 (d, 1H, CH, $^{3}J_{H-H}$ = 12.3); 7.03 (s, 1H, OH); 7.15-7.45 (m, 4H, 4Ar−H); 9.00 (s, 1H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): 13.95 ($\underline{CH_3}CH_2$), 39.64 ($\underline{CH}$−CN), 41.92 ($\underline{CH}$−Ar), 48.21 ($\underline{CH_2}Cl$), 50.36 ($\underline{CH}$−COO), 60.82 ($\underline{CH_2}O$), 82.85 (O−$\underline{C_{tert}}$), 115.59 (CH_{arom}), 115.87 (CH_{arom}), 117.31 (CN), 130.66 (CH_{arom}), 130.76 (CH_{arom}), 135.50-135.53 ($C_{ar.}$), 160.34-163.57 (F−$\underline{C_{ar.}}$), 163.75 (N−$\underline{C}$=O), 167.95 (O−$\underline{C}$=O).

Ethyl2-(chloromethyl)-5-cyano-2-hydroxy-6-oxo-4-(thiophen-2-yl)piperidine-3-carboxylate (11): Similar with synthesis of compound **10**, but use 0.91 g (0.0051 mol) 2-cyano-3-(thiophen-2-yl)acrylamide. Yield 1.49 g, 85.14%. $T_{mp.}$ = 165°C.

^{1}H NMR (300 MHz, DMSO-d_6): 0.93 (t, 3H, CH_3, $^{3}J_{H-H}$ = 6.9); 3.16 (d, 1H, CH, $^{3}J_{H-H}$ = 4.5); 3.67 (s, 3H, $\underline{CH_2}Cl$); 3.89 (k, 2H, $\underline{CH_2}O$, $^{3}J_{H-H}$ = 6.6); 4.18 (t, 1H, CH−Ar, $^{3}J_{H-H}$ = 12.6); 4.51 (d, 1H, CH, $^{3}J_{H-H}$ = 12); 7.00 (s, 1H, OH); 6.98-7.43 (m, 3H, $3CH_{thienyl}$); 9.01 (s, 1H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): 14.04 ($\underline{CH_3}CH_2$), 35.54 ($\underline{CH}$−CN), 42.91 ($\underline{CH}$−Ar), 48.16 ($\underline{CH_2}Cl$), 51.57 ($\underline{CH}$−COO), 60.95 ($\underline{CH_2}O$), 82.74 (O−$\underline{C_{tert}}$), 117.32 (CN), 125.62 ($CH_{thienyl}$), 126.49 ($CH_{thienyl}$), 127.50 ($CH_{thienyl}$), 141.93 ($C_{thienyl}$), 163.41 (N−$\underline{C}$=O), 167.83 (O−$\underline{C}$=O).

References

Adib, M., Rajai-Daryasarei, S., & Zhu, L.G. (2018). An efficient one-pot, multi-component diastereoselective synthesis of functionalized cyclopenta [c] chromenes. *Tetrahedron Letters*, *59*(39), 3550-3553.

Bardasov, I.N., Alekseeva, A.U., Chunikhin, S.S., Shishlikova, M.A., & Ershov, O.V. (2019). Synthesis and characterization of 2-(4-aryl-3-cyano-6-methylpyridin-2(1H)-ylidene)malononitriles, *Tetrahedron Letters*, *60*(17), 1170-1173.

Feng, X., Wang, Q., Lin, W., Dou, G.-L., Huang, Zh.-B., & Shi, D.-Q. (2013). Highly Efficient Synthesis of Polysubstituted Pyrroles via Four-Component Domino Reaction, *Organic Letters*, *15*(10), 2542-2545.

Gopalakrishnan, M., Thanusu, J., & Kanagarajan, V. (2009). A facile solid-state synthesis and in vitro antimicrobial activities of some 2,6-diarylpiperidin/tetrahydrothiopyran and tetrahydropyran-4-one oximes, *Journal of Enzyme Inhibition and Medicinal Chemistry*, *24*(3), 669–675.

Jadhav, A.M., Balwe, S.G., Kim, J.S., Lim, K.T., & Jeong, Y.T. (2019). Indium(III)chloride catalyzed synthesis of novel 1H-pyrazolo[1,2-b]phthalazine-5,10-diones and 1H-pyrazolo[1,2-a]pyridazine-5,8-diones under solvent-free condition, *Tetrahedron Letters*, *60*(7), 560-565.

Kanagarajan, V., Ezhilarasi, M.R., & Gopalakrishnan, M. (2011). Synthesis and in vitro microbiological evaluation of novel diethyl 6,6′-(1,4-phenylene)bis(4-aryl-2-oxo-cyclohex-3-enecarboxylates), *Journal of Enzyme Inhibition and Medicinal Chemistry*, *26*(4), 498-505.

Kiruthika, S.E., Lakshmi, N.V., Banu, B.R., & Perumal, P.T. (2011). A facile strategy for the one pot multicomponent synthesis of spiro dihydropyridines from amines and activated alkynes. *Tetrahedron Letters*, *52*(48), 6508-6511.

Lakshmi, N.V., Josephine, G.A.S., & Perumal, P.T. (2012). Novel route to spiropiperidines using N-methyl-4-piperidone, malononitrile and electrophiles, *Tetrahedron Letters*, *53*(10), 1282-1286.

Li, M., Lv, X.L., Wen, L.R., & Hu, Z.Q. (2013). Direct solvent-free regioselective construction of pyrrolo [1, 2-a][1, 10] phenanthrolines based on isocyanide-based multicomponent reactions. *Organic Letters*, *15*(6), 1262-1265.

Mukhopadhyay, Ch., Das, P., & Butcher, R.J. (2011). An Expeditious and Efficient Synthesis of Highly Functionalized [1,6]-Naphthyridines under Catalyst-Free Conditions in Aqueous Medium. *Organic Letters*, *13*(17), 4664-4667.

Naghiyev, F.N. (2019). Research into one-step three component reaction of some ylidenecyano-acetamides (or ylidenemalononitriles), malononitrile and 1,3-diaminopropane. *Chemical Problems*, *2*(17), 275-281.

Naghiyev, F.N. (2019). The investigation of michael addition of acetoacetanilide and methyl acetopyruvate to some ylidenecyanoacetamides. *Azerbaijan Chemical Journal*, *2*, 35-39.

Naghiyev, F.N., Asgarova, A.R., Maharramov, A.M., Rahimova, A.G., Akhundova, M.A. & Mamedov, I.G. (2020). Synthesis and antimicrobial properties of some thiazole and pyridine derivatives, *New Mat. Compd. Appl.*, *4(*1), 5-9.

Nguyen, H.T., Kim, S., Yu, N.H., Park, A.R., Yoon, H., Bae, C.H., ... & Kim, J.C. (2019). Antimicrobial activities of an oxygenated cyclohexanone derivative isolated from Amphirosellinia nigrospora JS-1675 against various plant pathogenic bacteria and fungi. *Journal of Applied Microbiology*, *126*(3), 894-904.

Pal, S., Khan, Md.N., Karamthulla, Sh., & Choudhury, L.H. (2015). Synthesis of pyranocoumarin fused spirooxindoles via Knoevenagel/Michael/cyclization sequence: a regioselective organocatalyzed multicomponent reaction, *Tetrahedron Letters*., *56*(2), 359-364.

Qiu, G., Ding, Q., Peng, Y., & Wu, J. (2010). Synthesis of (Z)-1-benzylidene-3-(1H-indol-1-yl)-1H-indene-2,2(3H)-dicarbonitriles via three-component reaction of 2-alkynylbenzaldehyde, malononitrile, and indole, *Tetrahedron Letters*, *51*(33), 4391-4394.

Quiroga, J., Cisneros, C., Insuasty, B., Abonía, R., Nogueras, M., & Sánchez, A. (2001). A regiospecific three-component one-step cyclocondensation to 6-cyano-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-ones. Using microwaves under solvent-free conditions, *Tetrahedron Letters*, *42*(33), 5625-5627.

Tahmassebi, D., Bryson, J.A., & Binz, S.I. (2011). 1,4-Diazabicyclo[2.2.2]octane as an Efficient Catalyst for a Clean, One-Pot Synthesis of Tetrahydrobenzo[b]pyran Derivatives via Multicomponent Reaction in Aqueous Media. *Synthetic Communications*, *41*(18), 2701-2711.

Tisseh, Z.N., Ahmadi, F., Dabiri, M., Khavasi, H.R., & Bazgir, A. (2012). A novel organocatalytic multi-component reaction: an efficient synthesis of polysubstituted pyrano-fused spirooxindoles, *Tetrahedron Letters*, *53*(28), 3603-3606.