Egypt. J. Chem. **Vol. 65,** No. SI13B pp. 1547 - 1551 (2022)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis and Antibacterial Evaluation of New developed 2,3-Dihydroquinazolin-4(1H)-ones

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Abstract

Antibacterial agents structurally based on quinazolin-4-one pharmacophore, have been designed and synthesized. Where the targeted compounds **5a, c** and **6a-c** were *in vitro* screened against three gram positive and three gram negative bacteria strains compared to ciprofloxacin as reference drug. Most of compounds had moderate antibacterial activity while compound **5c** showed the most significant activity and could be considered as a new lead compound for antibacterial drug design.

Keywords: Quinazolinone; antibacterial

1. Introduction

Quinazolinones are important core structure with a variety of biological activities as analgesic [1], anti-inflammatory [2], antifungal [3] antimycobacterial [4, 5], anticancer [6, 7] and antibacterial [8-13]. Antibacterial activity of quinazolinones is demonstrated via various mechanisms as PBP inhibitors [8], DNA inhibition [9], Mur A inhibitors [10], inhibition of tubulin polymerization [11] and DNA gyrase inhibitors [12]. Also 2,3 disubstituted quinazolinones have been evaluated as new antibacterial agents in many literatures [13-16] . Substitution at position- 2 with either methyl, phenyl or even unsubstituted **(I)** was found to be favoured for antibacterial activity [14]. In addition, it has been reported that if the 3-position has *p*- substituted phenyl ring will enhance the antibacterial activity **(II,III)** [15, 16].

Considering the aforementioned, our rationale is to design and synthesize new antibacterial quinazolinone where we combined the advantage of the substitutions at both 2 and 3 positions as position-2 was either unsubstituted or substituted with methyl or phenyl moieties and position-3 carrying *p*-substituted phenyl ring. We changed this *para* substitution with either acetyl or hydrazone moieties in order to investigate their effect on the antibacterial activity. (As shown in Figure 1)

The targeted compounds **5a,c** and **6a-c** are designed and evaluated as antibacterial agents against six bacterial strains (three gram positive and three gram negative). The most potent compound is **5c** which showed broad spectrum activity towards the all tested bacterial strains comparable to the standard ciprofloxacin and which will be considered as a new antibacterial lead compound.

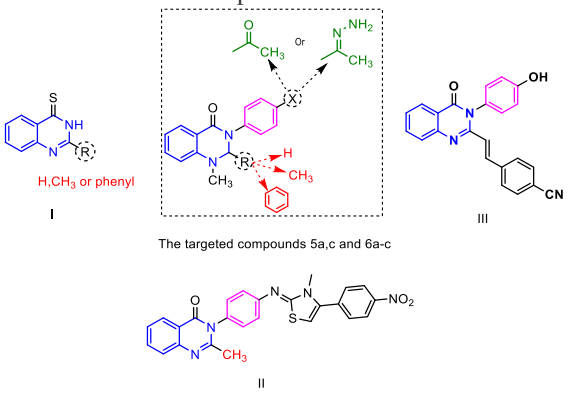

Figure 1: Reported antibacterial quinazolines and rationale design of the targeted compounds 5a,c and 6a-c

2. Experimental

2.1. Chemistry

Chemicals and reagents were purchased from Alfa- Asser Organics, Trading dynamic company and sigma Aldrich with high purity and used without further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel 60 GF254 purchased from E-Merck, Germany and visualized by UV-lamp at wave length (λ) 254 nm. Melting points (°C) were measured on a Gallenkamp apparatus (UK)

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Receive Date: 17 July 2019, Revise Date: 08 August 2019, Accept Date: 12 March 2023

DOI: 10.21608/EJCHEM.2023.14892.1905

and the results are uncorrected.[1]HNMR spectra were recorded on Bruker (High performance Digital FT-NMR Spectrometer Avance III 400MHz) at 400 MHz at the Faculty of Pharmacy, Cairo University, Egypt. Elemental and mass analyses were performed at the Regional Center for Mycology and Biotechnology, Faculty of pharmacy Al-Azhar University.

Preparation of *2-(methylamino)benzoic acid* 2: [17, 18]

Anthranilic acid (20 gm, 0.146 mole) was added portion-wise to a stirred solution of Na_2CO_3 (7.7 gm, 0.073 mole) in 200 ml water, the mixture was continued to stir for 30 minutes at room temperature. The reaction mixture was filtered then dimethyl sulfate (18.39 gm, 0.146 mole) was added to the filtrate and the reaction mixture was stirred for further 30 minutes. The formed solid was collected by vacuum filtration, washed with water and dried. The resulting 2-(methylamino)benzoic acid **2** was used in the next step without further purification. Yield= 65%, M.P. 168-170 °C as reported [17, 18]

Preparation of *1-methyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione* 3: [19, 20]

A mixture of 2-(methylamino)benzoic acid (**2**, 5 gm, 0.033 mole) in ethyl chloroformate 10 ml was refluxed for 4 hrs, then the mixture was cooled and the formed crystals was filtered and washed several times with petroleum ether then dried to obtain the desired product **3**. Yield= 51.7%, M.p.175-180°C as reported [19, 20].

Preparation of *N-(4-acetylphenyl)-2-(methylamino)benzamide* 4: [21-23]

A mixture of 1-methyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (**3**, 5 gm, 0.0028 mole) and *p*-aminoacetophenone (3.8 gm, 0.028 mole) in glacial acetic acid (50 ml) was refluxed for 4 hrs. The solution was cooled then poured into distilled water and the yellowish green solid formed was filtered and washed with water then dried to obtain the desired product **4**, which has yellowish green color, yield= 83%, M.p.175-176°C as reported [21-23].

General procedure for synthesis of *3-(4-acetylphenyl)-1-methyl-2-substituted-2,3-dihydroquinazolin-4(1H)-one* 5a-c:

A mixture of N-(4-acetylphenyl)-2-(methylamino)benzamide (**4**, 5 gm, 0.0186 mole) and an appropriate aldehyde (0.0186 mole) in a suitable solvent (ethanol (70 ml) /1-2 ml glacial acetic acid for compounds **5a, b** and glacial acetic acid (50 ml) for compound **5c**) was refluxed 18 hrs. The reaction mixture was allowed to cool, the formed crystals were collected and dried to obtain the desired product (**5a, c**). Compound **5b** was separated as sticky material which used in the next step without further purification. The product **5c** was further crystallized from dioxane.

3-(4-acetylphenyl)-1-methyl-2,3-dihydroquinazolin-4(1H)-one **5a**:[22]

White solid, yield= 50%, M.p.150-153°C (as reported)[22], MS: (m/z) = 280.25 [M+, 100%]. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.01; H, 5.89; N, 10.23

3-(4-acetylphenyl)-1-methyl-2-phenyl-2,3-dihydroquinazolin-4(1H)-one **5c**:

Yellow powder, yield= 32.2 %, M.p.167-170°C, **^{1}H NMR** (400 MHz, $CDCl_3$, *d*) δ 2.59, 2.63 (3H,2s, CH_3), 3.03 (3H, s, NCH_3), 5.90 (1H, s, NCHN), 6.65 (1H, d, *J*=8.2, ArH), 6.94 (1H, t, J=7.6, ArH), 7.24-7.37 (4H, m, ArH), 7.40-7.45 (3H, m, ArH), 7.95 (2H, d, *J*=8.56, ArH), 8.10 (1H, d, *J*=7.72, ArH). MS: (m/z) = 356.18 [M+, 68.58 %]. Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.28; H, 5.83; N, 8.09

General procedure for synthesis of *3-(4-(1-Hydrazonoethyl)phenyl)-1-methyl-2-un/substituted-2,3-dihydroquinazolin-4(1H)-one* 6a-c.

A mixture of the appropriate 3-(4-acetylphenyl)-1-methyl-quinazolinone derivatives **5a-c** (0.01 mole) and hydrazine hydrate (0.07 mole) in ethanol was heated under reflux (2 hrs for compound **4a** & 18 hrs for **4b-c**) then the reaction mixture was allowed to cool and the crystals allowed to be formed, the crystals was filtered, washed with small amount of methanol and dried to obtain the desired products **6a-c**.

(E,Z)-3-(4-(1-hydrazonoethyl)phenyl)-1-methyl-2,3-dihydroquinazolin-4(1H)-one **6a**:

Off white fluffy crystals, yield= 83.3%, M.p.173°C, **^{1}H NMR** (400 MHz, $CDCl_3$, *d*) δ 2.16, 2.35 (3H,2s, CH_3), 2.99, 3.00 (3H, 2s, NCH_3), 4.84, 4.89 (2H, 2s, NCH_2N), 5.40 (2H, bs, NH_2 exch.), 6.81 (1H, t, *J*=8.08, ArH), 6.96-7.01 (1H, m, ArH), 7.37-7.49 (3H, m, ArH), 7.71 (2H, d, *J*=8.44, ArH), 8.10 (1H, d, *J*=7.72, ArH). MS: (m/z) = 294.27 [M+, 88.62 %]. Anal. Calcd for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.58; H, 6.29; N, 19.27

(E,Z)-3-(4-(1-hydrazonoethyl)phenyl)-1,2-dimethyl-2,3-dihydroquinazolin-4(1H)-one **6b**:

Pale yellow crystals, yield= 35 %, M.p.189-192°C, **^{1}H NMR** (400 MHz, $CDCl_3$, *d*) δ 1.38 (3H, d, *J*=6.04, $CH\underline{CH_3}$), 2.15, 2.35 (3H,2s, CH_3), 2.97, 3.00 (3H, 2s, NCH_3), 5.02 (1H, q, *J*=12.08, NCHN), 5.41 (2H, bs, NH_2 exch.), 6.71 (1H, d, *J*=8.12, ArH), 6.92 (1H, t, *J*=7.28, ArH), 7.40-7.52 (3H, m, ArH), 7.72 (2H, d, *J*=8.6, ArH), 8.05 (1H, d, *J*=7.72, ArH). MS: (m/z) = 308.18 [M+, 32.81%]. Anal. Calcd for $C_{18}H_{20}N_4O$: C, 70.11; H, 6.54; N, 18.17. Found: C, 70.39; H, 6.75; N, 18.04

(E,Z)-3-(4-(1-hydrazonoethyl)phenyl)-1-methyl-2-phenyl-2,3-dihydroquinazolin-4(1H)-one **6c**:

Yellow crystals, yield= 30.4%, M.p.173-176°C, **^{1}H NMR** (400 MHz, $CDCl_3$, *d*) δ 2.11, 2.29 (3H,2s, CH_3), 2.96, 3.00 (3H, 2s, NCH_3), 5.37 (2H, bs, NH_2 exch.), 5.82, 5.87 (1H, 2s, NCHN), 6.61 (1H, d, *J*=8.16, ArH), 6.91 (1H, t, J=7.4, ArH), 7.21-7.32 (7H, m, ArH), 7.41 (1H, t, *J*=7.4, ArH), 7.62 (2H, d, *J*=8.48, ArH), 8.10 (1H, d, *J*=7.56, ArH). MS: (m/z) = 370.32

[M+, 100 %]. Anal. Calcd for $C_{23}H_{22}N_4O$: C, 74.57; H, 5.99; N, 15.12. Found: C, 74.33; H, 6.18; N, 15.38

2.2. Antibacterial activity

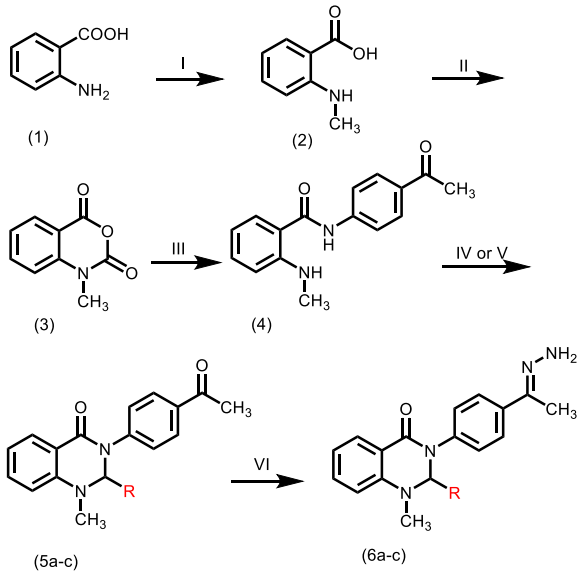
Antibacterial activities were performed at the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Cairo, Egypt.

The MICs of the targeted compounds were obtained using the micro-dilution method [24]. Where the microbial inoculates were prepared, and the suspensions were adjusted to 10^6 CFU/mL. The compounds and the standard drug (Ciprofloxacin) were dissolved in dimethyl sulfoxide (DMSO). Then, two fold dilutions were performed in a 96 well plate. Each well of the microplate included 40 µL of the growth medium brain heart infusion (BHI), 10 µL of inoculum, and 50 µL of the diluted compounds and the standard. DMSO was used as a negative control. The plates were incubated at 37 °C for 24 h. After that, 40 µL of tetrazolium salt (2,3-bis[2-methyloxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxanilide) (XTT) was added to the wells. The plates were incubated at 37°C for 1 h in a dark place, after which colorimetric change in the XTT reduction assay was measured using a microtiter plate reader (Tecan Sunrise absorbance reader; Tecan UK, Reading, United Kingdom) at 492 nm. The lowest concentration that completely inhibited microbial growth was taken as the MIC [25]. All experiments were performed in triplicate.

3. Results and discussion

3.1. Chemistry

Our targeted compounds **5a,c** and **6a-c** were prepared according to the defined scheme 1. Using a reported procedure, N-methyl isatoic anhydride **3**; the starting material; was refluxed for 4 hrs with *p*-aminoacetophenone in glacial acetic acid to produce the benzamide intermediate **4** [21-23]. Benzamide **4** is a versatile intermediate for the synthesis of different quinazolinones derivatives [26-28]. The benzamide intermediate **4** was identified by matching its M.p. with the reported one [22] and incorporation in the formation of the 2,3-dihydroquinazolin-4(1H)-one derivatives **5a-c**. Cyclization of benzamide **4** with three aldehydes resulted in formation of 2,3-dihydroquinazolin-4(1H)-one derivatives **5a-c**. The difference in aliphatic and aromatic aldehydes reactivity investigates the using of different solvents where acidified ethanol was used either with formaldehyde or acetaldehyde while glacial acetic acid was used in case of benzaldehyde. The chemical structure of the 2,3-dihydroquinazolin-4(1H)-one derivatives **5a-c** was defined by matching the M.p. of **5a** with its reported one in addition to mass and elelmental analysis , while the compound **5c** was identified by ^{1}H NMR, mass spectra in addition to elemental analysis. ^{1}H NMR spectrum of 3-(4-Acetylphenyl)-1-methyl-2-phenyl-2,3-dihydroquinazolin-4(1H)-one **5c** revealed the appearance of 2,3-dihydroquinazolin-4(1H)-one-2H as singlet peak at δ= 5.90 ppm. The identity 3-(4-acetylphenyl)-1,2-dimethyl-2,3-dihydroquinazolin-4(1H)-one **5b** was achieved by incorporation in the next reaction due to difficulty of purification. Hyrazones **6a-c** were prepared by condensation of 2,3-dihydroquinazolin-4(1H)-one derivatives **5a-c** with excess hydrazine hydrate in ethanol. Where the chemical structure of the hydrazone intermediates **6a-c** was identified by using instrumental analysis including ^{1}HNMR, mass spectra in addition to elemental analysis. The ^{1}H NMR showed the appearance of broad singlet peaks at (δ=5.40 for **6a**, 5.41 for **6b** and 5.37 for **6c**) which indicates the protons of NH_2 group. The presence of azomethene group resulted in *Z* and *E* geometrical isomers which is difficulty separated and affects the splitting of the ^{1}HNMR peaks of adjacent methyl, N- methyl and 2,3-dihydroquinazolin-4(1H)-one-2H – protons [29, 30].



5a , 6a R=H
5b , 6b R=CH_3
5c , 6c R=C_6H_5

Scheme 1 for target compounds, reagents and conditions: (I) Na_2CO_3, water, stirr on cold for 1 hr, dimethylsulfate, stir on cold 1 hr; (II) ethylchloroformate, reflux 4 hrs; (III) *p*-aminoacetophenone, glacial acetic acid, reflux 4hrs; (IV) for 5a,b appropriate aldehyde, absolute ethanol, drops of glacial acetic acid, reflux overnight; (V) for 5c, appropriate aldehyde, glacial acetic acid, reflux overnight; (VI) hydrazine hydrate, absolute ethanol, reflux 2hrs for 6a, reflux overnight for 6b,c.

3.2. Antibacterial activity

The targeted quinazolinones **5a,c** and **6a-c** were *in vitro* evaluated for their antibacterial activities by measuring MIC using microtiter assay against six bacterial strains obtained from the American Type Culture Collection; three gram-positive bacteria: *Staphylococcus aureus* (ATCC 6538), *Staphylococcus epidermidis* (ATCC 12228) and *Enterococcus faecalis* (ATCC 29212) three gram-negative bacteria: *klebsiella pneumoniae* (ATCC 13883), *proteus mirabilis* (ATCC 12453) and *salmonella typhimurium* (ATCC 14028) using the ciprofloxacin as reference.

As shown in Table **1**, Most of compounds showed promising antibacterial activity. Compound **5c** displayed the most significant antibacterial activity against all the bacterial strains with MIC values ranging from 1.95 to 7.81 µg/mL. Compound **5a** showed good antibacterial activity against two gram positive bacteria *Staphylococcus aureus* and *Enterococcus faecalis* with MIC value 15.63 µg/mL while showed moderate activity against two gram negative bacteria *klebsiella pneumonia* , *salmonella typhimurium* and one gram positive bacterium *Staphylococcus epidermidis* with MIC value 31.25 µg/mL. Compound **6b** showed moderate activity against two gram positive bacteria *Staphylococcus epidermidis* and *Enterococcus faecalis* with MIC value 31.25 µg/mL and two gram negative bacteria *klebsiella pneumoniae* and *salmonella typhimurium* with MIC value 31.25 µg/mL. Compound **6c** showed moderate activity against *salmonella typhimurium* with MIC value 31.25 µg/mL. Compound **6c** was the least active one against all the six bacterial strains.

Table 1. Antibacterial activity as MICs (µg/mL) of tested compounds 5a,c and 6a-c against six bacterial strains.

Comp	Gram positives bacteria MICs (µg/mL)			Gram negative bacteria MICs (µg/mL)		
	S. aureus	*S. epidermidis*	*E. faecalis*	*k. pneumoniae*	*p. mirabilis*	*Sal. typhimurium*
5a	15.63	31.25	15.63	31.25	62.5	31.25
5c	1.95	7.81	3.9	1.95	7.81	3.9
6a	250	125	250	62.5	250	125
6b	125	31.25	31.25	31.25	62.5	31.25
6c	250	125	125	62.5	62.5	31.25
Cipro.	**0.98**	**1.95**	**0.98**	**0.98**	**3.9**	**1.95**

4. Conclusions

In the current work, quinazolinones **5a,c** and **6a-c** have been synthesized and screened as new antibacterial agents against six bacterial strains. Most of these compounds show good to moderate antibacterial activity. Among the tested compounds, **5c** was the most active one as it showed a broad spectrum activity and could be considered as a new lead compound in antibacterial drug design.

5. Conflicts of interest

There are no conflicts to declare.

6. Acknowledgments

A great thanks to Dr. Marwa M. Emam at the Regional Center for Mycology and Biotechnology for her collaboration in performing the biological activity.

References

[1] Alagarsamy, V., et al., Synthesis and pharmacological investigation of some novel 2,3-disubstituted quinazolin-4(3H)-ones as analgesic and antiinflammatory agents. Pharmazie, 2003. 58(4): p. 233-6.
[2] Elfeky, s., et al., Ultrasound one pot synthesis of fused quinazolinones and quinazolinediones, screening and molecular docking study as phosphodiesterase 7A inhibitors. Egyptian Journal of Chemistry, 2019: p. -.
[3] Lakhan, R. and B.J. Rai, Synthesis of some new 3-(2'-benzothiazolyl)-4(3H)-quinazolinones as antifungal agents. Journal of Chemical & Engineering Data, 1986. 31(4): p. 501-502.
[4] Mirchi, A., N. Sizochenko, and J. Leszczynski, Fullerene quinazolinone conjugates targeting Mycobacterium tuberculosis: a combined molecular docking, QSAR, and ONIOM approach. Structural Chemistry, 2018. 29(3): p. 765-775.
[5] Pandit, U. and A. Dodiya, Synthesis and antitubercular activity of novel pyrazole–quinazolinone hybrid analogs. Medicinal Chemistry Research, 2013. 22(7): p. 3364-3371.
[6] Dohle, W., et al., Quinazolinone-Based Anticancer Agents: Synthesis, Antiproliferative SAR, Antitubulin Activity, and Tubulin Co-crystal Structure. J Med Chem, 2018. 61(3): p. 1031-1044.
[7] Thakral, S., et al., A synthetic approach and molecular docking study of hybrids of quinazolin-4-ones and thiazolidin-4-ones as anticancer agents. Medicinal Chemistry Research, 2017. 26(8): p. 1595-1604.
[8] Bouley, R., et al., Structure–Activity Relationship for the 4(3H)-Quinazolinone Antibacterials. Journal of Medicinal Chemistry, 2016. 59(10): p. 5011-5021.
[9] Peng, X.-M., et al., Quinazolinone azolyl ethanols: potential lead antimicrobial agents with dual action modes targeting methicillin-resistant Staphylococcus aureus DNA. Future Medicinal Chemistry, 2016. 8(16): p. 1927-1940.
[10] Hrast, M., et al., Synthesis and structure–activity relationship study of novel quinazolinone-based inhibitors of MurA. Bioorganic & Medicinal Chemistry Letters, 2017. 27(15): p. 3529-3533.
[11] Hour, M.-J., et al., 6-Alkylamino- and 2,3-Dihydro-3‘-methoxy-2-phenyl-4-quinazolinones and Related Compounds: Their Synthesis, Cytotoxicity, and Inhibition of Tubulin Polymerization. Journal of Medicinal Chemistry, 2000. 43(23): p. 4479-4487.

[12] Boyapati, S., et al., Synthesis, Antimicrobial Evaluation, and Docking Studies of Novel 4-Substituted Quinazoline Derivatives as DNA-Gyrase Inhibitors. Archiv der Pharmazie, 2010. 343(10): p. 570-576.
[13] Arsanious, M., et al., Synthesis and Antimicrobial Evaluation of New 2-Methylquinazolin-4(3H)-one Phosphorothioates. Egyptian Journal of Chemistry, 2019.
[14] Antypenko, L., et al., 2-Alkyl(aryl)-quinazolin-4(3H)-thiones, 2-R-(quinazolin-4(3H)-ylthio)carboxylic acids and amides: synthesis, molecular docking, antimicrobial and anticancer properties. Journal of Enzyme Inhibition and Medicinal Chemistry, 2016. 31(2): p. 253-265.
[15] Hassan, H.Y., A.A. Ismaiel, and H.A.H. El-Sherief, Studies on synthesis of some quinazolinones bearing different heterocyclic moieties with expected biological activity. European Journal of Medicinal Chemistry, 1991. 26(7): p. 743-748.
[16] Gatadi, S., et al., Synthesis of new 3-phenylquinazolin-4(3H)-one derivatives as potent antibacterial agents effective against methicillin- and vancomycin-resistant Staphylococcus aureus (MRSA and VRSA). Bioorg Chem, 2018. 81: p. 175-183.
[17] Pastor G., et al., Bull. Soc. Chem. Fr. II-Chemie., 1926. 16.
[18] Huben J. and Brassert W., Ber. Deut. Chem. Ges. , 1906(39).
[19] Niak, N., A. Amin, and S. Patel, Synthesis and spectral study of 1-Methyl-2 (R)-1,4-dihydro-4-oxoquinazoline derivatives. chemischer informationsdienst, 1980. 11(9): p. no-no.
[20] Hardtmann, G.E., G. Koletar, and O.R. Pfister, The chemistry of 2H-3,1-benzoxazine-2,4(1H)dione (isatoic anhydrides) 1. The synthesis of N-substituted 2H-3,1-benzoxazine-2,4(1H)diones. Journal of Heterocyclic Chemistry, 1975. 12(3): p. 565-572.
[21] Coyne, W.E. and J.W. Cusic, 3,4-Dihydro-2(1H)-quinazolinones. Journal of Medicinal Chemistry, 1968. 11(6): p. 1208-1213.
[22] S. M. Sakr, Zagazig J. Pharm. Sci, 2003. 12: p. 24-28.
[23] El-Sabbagh, O.I., et al., Synthesis of new 2,3-dihydroquinazolin-4(1H)-one derivatives for analgesic and anti-inflammatory evaluation. Arch Pharm (Weinheim), 2010. 343(5): p. 274-81.
[24] Tunney, M.M., et al., Rapid colorimetric assay for antimicrobial susceptibility testing of Pseudomonas aeruginosa. Antimicrob Agents Chemother, 2004. 48(5): p. 1879-81.
[25] Mohammed, H.A., M.M. Abdel-Aziz, and M.M. Hegazy, Anti-Oral Pathogens of Tecoma stans (L.) and Cassia javanica (L.) Flower Volatile Oils in Comparison with Chlorhexidine in Accordance with Their Folk Medicinal Uses. Medicina (Kaunas), 2019. 55(6).
[26] Monireh Shakiba Nahad and G.M. Ziarani, One-pot Synthesis of Quinazolinone and Benzamide Derivatives Using SBA-Pr-SO3H as a Nanoporous Heterogeneous Acid Catalyst. Oriental Journal of Chemistry, 2013. 29(4): p. 1597-1603.
[27] Liu, Z., et al., "On-Water" Synthesis of Quinazolinones and Dihydroquinazolinones Starting from o-Bromobenzonitrile. Molecules (Basel, Switzerland), 2018. 23(9): p. 2325.
[28] Kamel, M., et al., Synthetic approaches and potential bioactivity of different functionalized quinazoline and quinazolinone scaffolds. Egyptian Pharmaceutical Journal, 2016. 15(3): p. 98-131.
[29] Lopes, A.B., et al., Characterization of amide bond conformers for a novel heterocyclic template of N-acylhydrazone derivatives. Molecules, 2013. 18(10): p. 11683-704.
[30] da Silva, T.F., et al., Novel orally active analgesic and anti-inflammatory cyclohexyl-N-acylhydrazone derivatives. Molecules, 2015. 20(2): p. 3067-88.